Mechanism of APC truncation involved in colorectal cancer tumorigenesis (Review)

TUYA WANG, JING FU, YE HUANG and CHUN FU

Department of Medicine, Hetao College, Bayannur, Inner Mongolia Autonomous Region 015000, P.R. China

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Abstract. Adenomatous polyposis coli (APC) is widely recognized as a heavily mutated gene that suppresses tumor growth in colorectal cancer (CRC). Its mutation is considered to be the primary and early event that occurs in the development of CRC. In addition, APC has a crucial role in inhibiting the canonical Wnt signaling pathway. APC mutations in CRC result in the production of shortened gene products. This impairment of β-catenin destruction complexes causes an accumulation of active β-catenin in the cytoplasm and nucleus. In these compartments, β-catenin can bind with DNA-binding proteins of the transcription factor/lymphoid enhancer-binding factor family, thereby activating the Wnt signaling pathway. Consequently, the balance of numerous cellular processes is disrupted, ultimately driving the formation of tumors. There is a growing body of evidence indicating the prevalent occurrence of APC truncation in the majority of CRC cases. Furthermore, it has been observed that these truncated proteins have a crucial role in the activation of the Wnt signaling pathway and the subsequent loss of tumor inhibitory function. This review aimed to provide an overview of the recent advancements in understanding the mechanism behind APC truncation and its association with the onset and progression of CRC.

Contents

Correspondence to: Dr Tuya Wang, Department of Medicine, Hetao College, 1 Yun Zhong Road, Linhe, Bayannur, Inner Mongolia Autonomous Region 015000, P.R. China
E-mail: htxywty2018@163.com

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1. Introduction

Colorectal cancer (CRC), which accounts for ~10% of all cancer cases, ranks second as a global cause of cancer-related fatalities (1). In China, CRC ranks third among malignant tumors and its occurrence is steadily rising, particularly among younger individuals (2). It is estimated that by 2030, the number of CRC cases under 50 years of age will account for 11% of the total number of colon cancer and 23% of the total number of rectal cancer cases (3). The advanced stage of most diagnosed cases of CRC can be attributed to the absence of early screening (4). Starting from the 1950s, significant changes in lifestyle factors, such as antibiotics consumption, decreased physical activity and increased obesity, have had an impact on the gut microbiome, potentially playing a significant role in the occurrence of CRC at a younger age (5,6). A molecular biology perspective highlights the significant involvement of colon epithelial proto-oncogene mutation, tumor suppressor gene inactivation and genome epigenetic modification in the initiation and progression of CRC (7).

In the development of CRC, the inactivation of the adenomatous polyposis coli (APC) gene, a crucial tumor suppressor gene, is regarded as an initial and significant step (8). The APC gene spans 8,535 nucleotides and is situated on chromosome 5q21-q22. It comprises 21 exons (9). The protein encoded by the APC gene is a large 310-kDa molecule, made up of 2,843 amino acids. A noticeable portion of the genetic code, ~75%, is found in exon 15, which is also the most frequently affected area for mutations in the APC gene. When there are mutations in the germ cells of the APC gene, it leads to familial adenomatous polyposis (FAP), a remarkable genetic predisposition to the development of CRC (10). More than 80% of sporadic CRC cases were discovered to have somatic APC gene mutations. APC is a versatile protein with multiple functions facilitated by various binding partners. The APC structure extends from its N-terminus to its C-terminus and includes an oligomerization region, an armadillo (ARM) repeat region, a domain with repeats of either 15 or 20 residues, a Ser-Ala-Met-Pro (SAMP) repeat domain, a basic domain and a domain that interacts with end-binding protein 1 (EB1) and Discs large homolog

(DLG) (Fig. 1) (11,12). Experimental evidence has illustrated that the binding site for APC mutants is the oligomerization domain. APC mutant proteins that retain at least the initial 171 amino acids can interact with this region, potentially leading to a dominant negative effect (13). The most highly conserved domain of APC proteins, known as the ARM repeat domain, has been proven to have the ability to bind with various proteins, including IQ motif containing GTPase activating protein 1, protein phosphatase type 2A and asef and kinesin-associated protein 3 (KAP3), which all contain IQ motifs and are associated with GTP enzyme activation.

These interactions noticeably affect the stimulation of cell migration and adhesion (14,15). The 15- or 20-residue repeat domain and the SAMP repeat sequence have a crucial function in negatively regulating the canonical Wnt signaling pathway by promoting the proteasome degradation of β-catenin (16,17). By interacting with EB1, the basic and C-terminal domains have the ability to directly or indirectly bind to microtubules, thereby preserving microtubule stability, ensuring proper kinetochore function and facilitating chromosome segregation (18). APC is involved in a wide range of cellular activities, such as cell growth, programmed cell death, movement, cell attachment, DNA fixing and separation of chromosomes. It achieves these functions by interacting with different proteins. Individuals with CRC have shorter versions of the APC protein that are missing specific regions needed for attaching to microtubules, EB1 and β-catenin. This deficiency causes an unstable genetic structure, leading to increased cell growth and decreased differentiation (19,20). A notable finding indicated that a remarkable percentage (73%) of metastatic CRC cases had an accumulation of APC mutations, the majority of which were truncated mutations. It was revealed that patients with N-terminal APC mutations had a notably lower tumor mutational burden than those with C-terminal mutations. In addition, patients with N-terminal APC mutations exhibited prolonged overall survival in comparison to those with C-terminal mutations. Further analysis of tumor gene pathways demonstrated that patients with C-terminal mutations had markedly higher frequency of gene mutations in the RTK/RAS, Wnt and TGF-β signaling pathways than patients with N-terminal mutations. In addition, the presence of KRAS proto-oncogene, GTPase, APC membrane recruitment protein 1, transforming growth factor (TGF)-β receptor type 2 and AT-rich interactive domain-containing protein 1A-driven mutations were found to be higher among patients with C-terminal APC mutations. Consequently, the truncation of the APC gene's C-terminal region, leading to the loss of its tumor suppressor function, may have a crucial role in CRC development (21). However, there have been preclinical animal studies demonstrating that the C-terminus of APC does not influence the formation or advancement of intestinal adenomas. Scholars developed two sets of mouse models by genetically altering them. In the first set, they deleted the SAMP repeat sequence while keeping the C-terminus intact. In the second set, they removed the entire C-terminus while maintaining the other domains. Surprisingly, both sets of mice developed numerous intestinal adenomas, which were similar in terms of quantity, placement and abnormal cell growth. Strikingly, no signs of cancer were detected in either set of mice. Although the tumors in mice showed a comparable disruption of the Wnt signaling pathway, there was no indication that the C-terminus had any functional differences. This includes aspects such as cell migration, chromosomal instability (CIN) or the localization of APC and EB1 (22). The Wnt/β-catenin signaling pathway, as detailed by Nusse and Clevers (23) and Klaus and Birchmeier (24), plays a crucial role in regulating cell fate, proliferation, migration and polarity. This pathway is activated when Wnt proteins bind to Frizzled receptors and low-density lipoprotein-related receptors 5 and 6 co-receptors, leading to the inhibition of the β-catenin destruction complex [comprising APC, Axin, glycogen synthase kinase 3β (GSK-3β) and casein kinase 1 (CK1)]. Consequently, β-catenin accumulates in the cytoplasm and translocates to the nucleus, where it interacts with transcription factor (TCF)/lymphoid enhancer-binding factor (LEF) transcription factors to regulate target gene expression. This signaling is essential for embryonic development, tissue homeostasis and stem cell renewal. However, aberrant activation of the Wnt/β-catenin pathway, often due to mutations in APC or β-catenin, is a key driver in the development of various cancers, including CRC. While the Hippo, Notch and Hedgehog pathways play significant roles in CRC progression, their relationship with APC truncations is less direct compared to the well-characterized impact of APC mutations on Wnt/β-catenin signaling (19). APC truncations primarily dysregulate Wnt signaling, driving tumorigenesis. Although dysregulation of the Hippo, Notch and Hedgehog pathways can contribute to CRC through various mechanisms, current evidence does not directly link APC truncations to the modulation of these pathways (20). Instead, their cooperative interaction with Wnt signaling, which is altered by APC truncations, may exacerbate cancer progression, with each pathway contributing to cellular proliferation, differentiation and metastasis in distinct manners (21).

Despite extensive research on APC's involvement in CRC, recent studies continued to reveal new dimensions of its role, emphasizing its ongoing relevance in the field of oncology. Emerging evidence highlights the intricate interactions of APC with various signaling pathways, its impact on CIN and its influence on the tumor microenvironment, all of which are crucial for developing novel therapeutic strategies. Given the extensive coverage of the canonical Wnt/β-catenin signaling pathway in the prior literature, the present review did not concentrate on this aspect. This review emphasized recent preclinical findings, particularly new insights from animal models that challenge previous assumptions about the C-terminal region of APC gene and its role in CRC formation and progression, as well as emerging evidence on the therapeutic implications of specific APC mutations. This review concentrated on the roles and implications of APC mutations beyond the well-established Wnt/β-catenin signaling pathway. While the canonical role of APC in the Wnt/β-catenin signaling pathway has been extensively studied, this review uniquely explored the multifaceted impact of APC truncation across various cellular processes, including cell adhesion, migration, apoptosis, DNA repair and CIN. By integrating these diverse pathways, this review aimed to provide a holistic view of APC's contribution to CRC progression and identify novel therapeutic targets. Specifically, it highlighted the differential impact of N-terminal and C-terminal truncations of the APC gene on tumor mutational burden, overall survival and

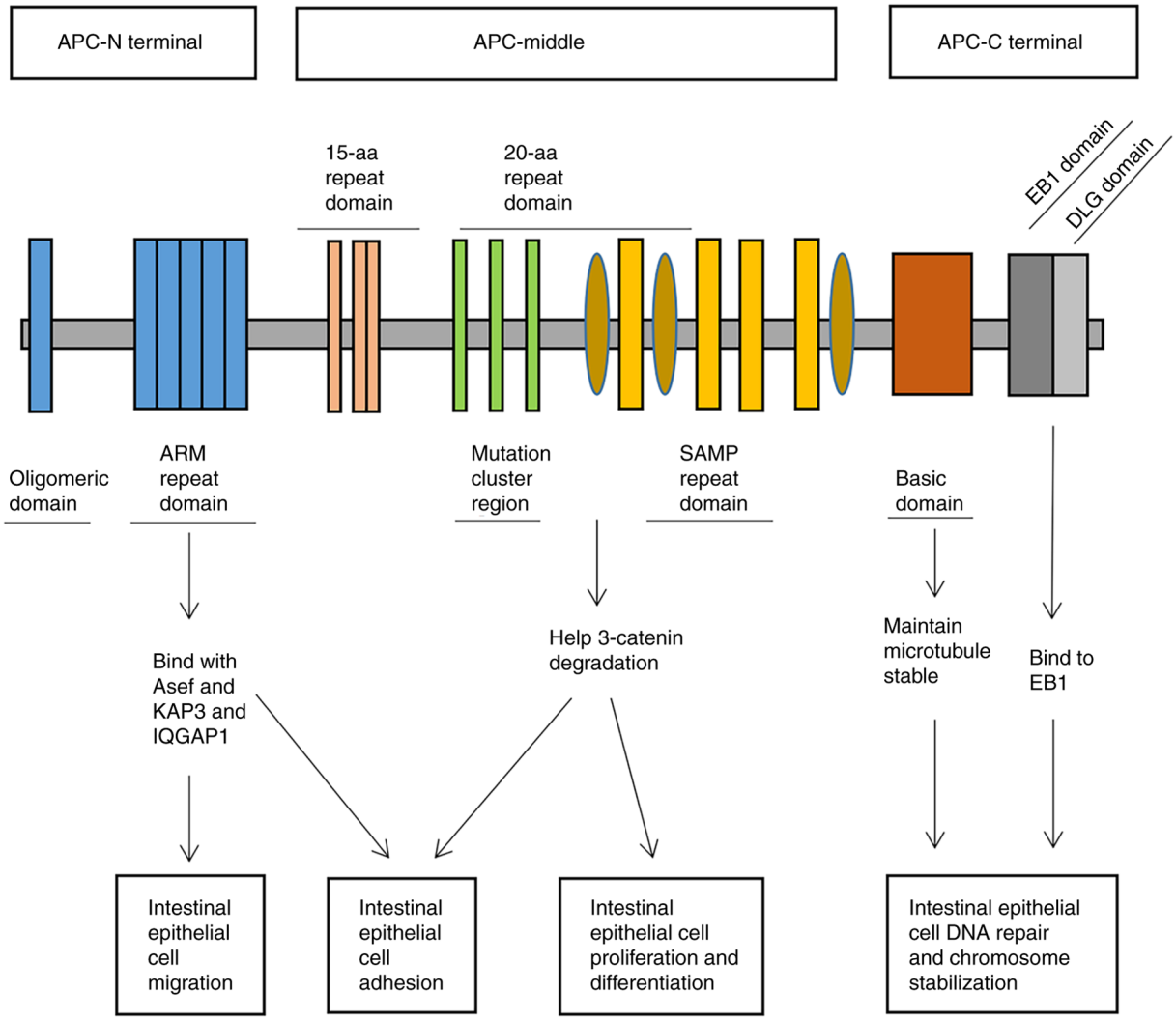

Figure 1. Structure of APC and its function and mechanism in intestinal epithelial cells. APC, adenomatous polyposis coli; EB1, end-binding protein 1; DLG, Discs large homolog; ARM, armadillo; SAMP, Ser-Ala-Met-Pro; KAP3, kinesin-associated protein 3; IQGAP1, IQ motif containing GTPase activating protein 1.

associated genetic mutations in patients with CRC. In addition, it explored the non-canonical roles of APC, including its interactions with various signaling pathways, such as RTK/RAS and TGF-β, its role in maintaining chromosomal stability and microtubule dynamics and its involvement in cell adhesion.

2. APC truncation and inactivation of the canonical Wnt signaling pathway

One of the most prevalent pathways mutated in cancer is the Wnt/β-catenin signaling pathway, which has a pivotal role in coordinating crucial processes during early embryonic development, tissue stability and regeneration, as well as governing the maintenance of stem cells, determination of cell fate and regulation of cell proliferation (23). The APC protein plays a crucial role in controlling cell proliferation and differentiation in the gastrointestinal tract by acting as a significant inhibitor of the canonical Wnt signaling pathway (Fig. 2) (25,26). To achieve this, cytoplasmic complexes involving β-catenin, APC and GSK-3β are necessary to facilitate serine phosphorylation and consequent degradation of β-catenin (27). GSK-3β, a kinase, is responsible for phosphorylating β-catenin and APC. The cooperation between the kinase and the substrate heavily relies on the presence of the APC protein. The formation of the complex β-catenin-GSK-3β-APC involves another protein called Axin (28). Under normal circumstances, the Wnt signaling pathway promotes the degradation of β-catenin by inhibiting GSK-3β activity. However, under pathological conditions, mutations in APC hinder β-catenin degradation (29,30). APC promotes AXIN1 multimerization and stabilizes the AXIN1 complex, thus increasing the efficiency of this disruption mechanism (31). In the canonical Wnt/β-catenin signaling pathway, the cytoplasmic protein β-catenin serves as a crucial switch. Its stability and level of activation are regulated by both the β-catenin disruption complex and the Wnt growth factor receptor. Within this intricate process, AXIN1, a protein known for suppressing tumor growth, functions as a scaffold by interacting with various molecules, such as β-catenin, APC and two serine-threonine kinases (CK1α/δ and GSK-3α/β). This interaction leads to the labeling of β-catenin for degradation by the proteasome through a process called phosphorylation-dependent ubiquitination (31,32). Furthermore, the involvement of

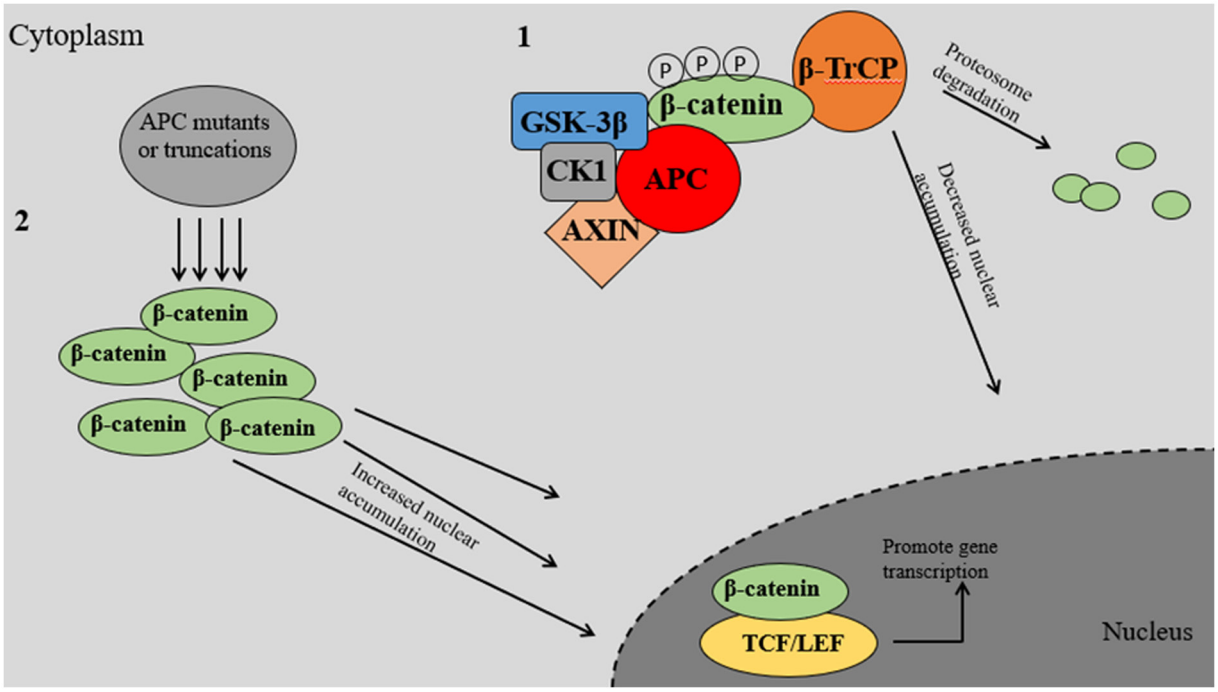

Figure 2. Schematic illustrating the negative regulation of the canonical Wnt signaling pathway by the cytoplasmic APC protein. The shift from the inactive state '1' to the active state '2' is determined by the nuclear buildup of β-catenin, a crucial factor. Once present in significant amounts within the nucleus, β-catenin interacts with TCF/LEF family transcription factors, leading to alterations in gene transcription. The active state '2' of the Wnt signaling pathway is a distinguishing trait of colorectal cancer cells, facilitating a proliferative and survival-friendly milieu for cancer cells. GSK-3β, glycogen synthase kinase 3β; CK1, casein kinase 1; TCF, transcription factor; LEF, lymphoid enhancer-binding factor; β-TrCP, β-transducin repeat-containing protein.

the Wnt growth factor receptor is crucial in the transformation of the disruption complex into the receptor-associated Wnt complex. In this scenario, the phosphorylation and ubiquitination of β-catenin are significantly diminished, leading to elevated levels of β-catenin and its accumulation in the nucleus. This, in turn, enhances the activation of β-catenin/TCF/LEF target genes. Within the disruption complex, the scaffold protein and tumor suppressor AXIN1 collaborate with APC to enlist casein kinase 1 (CK1) and GSK-3β, which ultimately affect the substrate β-catenin (33-35). AXIN1, a pivotal scaffold for the disruption complex, possesses the remarkable ability to directly associate and assemble all the constituent elements of the core disruptive complex. Furthermore, it markedly enhances the phosphorylation of β-catenin by impeding the phosphorylation of other molecules that via with β-catenin to a certain degree (36). APC, the second scaffold of the disruption complex, has the ability to bind to up to 10 β-catenin sites, some of which are controlled by kinase phosphorylation of the disruption complex. In addition, APC contains three docking motifs for AXIN1. Within a sequence of amino acid repeats binding β-catenin, the APC protein also includes three motifs for binding AXIN1 (37). The function of the β-catenin disruption complex heavily relies on the essential role of APC. When APC truncation mutations occur in intestinal stem cells, these mutations cause the loss of different motifs to varying degrees. As a result, the levels of β-catenin increase significantly, which has been linked to the occurrence and development of up to 80% of CRC cases.

The APC gene in colonic adenomas and CRCs is shortened, leading to the impairment of the β-catenin disruption complex. This results in the accumulation of active β-catenin in the cytoplasm and nucleus, where it can form complexes with TCF/LEF family DNA-binding proteins. As a result, β-catenin acts as a co-activator for TCF, assisting in transcriptional processes. However, in APC-mutant tumor cells, the regulatory proteins lose their ability to inhibit the Wnt signaling pathway, as they are either upstream or at the level of the APC protein in the pathway. The APC mutation causes an increase in the activation of β-catenin/TCF transcriptional activity by enhancing the levels of nuclear β-catenin and reducing the inhibitory effects of C-terminal-binding protein on the repressive complex. This activation results in the elevation of cyclin D1 and Myc, which play crucial roles in promoting cell proliferation, apoptosis and cell cycle progression, thus driving the development of tumors (38). The strong selectivity of the retention of the initial 20 amino acid repeat sequences of APC, which can bind to β-catenin and control its transcriptional activity, is strikingly favored. The selection of the APC genotype was specifically aimed at achieving a particular level of β-catenin, which is highly favorable for the development of tumors. However, in the absence of any binding sites between APC and β-catenin, the continuous activation of the β-catenin pathway may result in extensive alterations in gene regulation, consequently raising the likelihood of cell demise. By contrast, maintaining certain β-catenin binding sites could result in a partial decrease in activity, thereby enabling the Wnt signaling pathway to still confer a growth advantage to CRC tumor cells without triggering cell death (39). This led to the suggestion of the 'triple hit' hypothesis, which suggests that the optimal level of Wnt in CRC tumors may vary as the tumor progresses, either due to alterations in the surrounding environment or the acquisition of new genetic mutations (40).

Certain types of CRC can regulate the Wnt signaling pathway by modifying the copy numbers or experiencing other types of genetic alterations known as 'third hits' in APC genes. In addition, a different hypothesis called 'independent nuclear export activities' has been suggested, proposing that the truncation of APC reduces the ability to export proteins from the nucleus (41). This reduction is caused by the loss of the central nuclear export signal located next to the mutation cluster region, leading to a significant impairment of its tumor suppressor function (42).

APC mutations predominantly consist of missense mutations that introduce premature stop signals, causing a shortened APC protein to be produced. The majority of these mutations are found within a specific region known as the mutation-cluster region, which houses crucial binding sites for β-catenin, Axin and other important proteins involved in the Wnt signaling pathway. The truncation of APC due to these mutations disrupts essential interactions with Wnt signaling proteins, actin and the microtubule cytoskeleton that occur at the protein's C-terminus. Recent findings have solidified the notion that the truncation of APC produces irregular control over β-catenin, resulting in heightened transcription of Wnt target genes and consequently contributing to the onset and progression of CRC (43).

3. APC truncation and intestinal epithelial cell proliferation

The C-terminal binding protein (CtBP) plays a crucial role in the functional mechanism of APC in its ability to counteract β-catenin. *In vivo*, APC is present and interacts with CtBP through a conserved sequence comprising 15 amino acids. When APC is truncated, it loses its ability to bind to CtBP. Consequently, an increase in CtBP levels leads to the formation of a higher amount of β-catenin/TCF complexes and an elevation in TCF-mediated transcription. It is worth highlighting that *in vivo*, there is no association between CtBP and TCF, and mutating the CtBP binding motif in TCF-4 does not affect its transcriptional activity. This casts doubt on the notion that CtBP directly enhances TCF function. Evidence suggests that APC facilitates the interaction between β-catenin and CtBP, and CtBP hinders the binding of free nuclear β-catenin to TCF by forming a complex with APC/β-catenin (44). CtBP1 and CtBP2 are transcriptional co-regulators that have been conserved throughout evolution. They interact with DNA-binding transcription factors and chromatin remodeling factors, such as histone methyltransferases and histone deacetylases. This interaction allows them to either activate or suppress gene expression (45). Overexpression of CtBP1 and CtBP2 is frequently observed in various solid tumors, indicating that CtBP is a crucial gene involved in promoting cancer growth in solid tumors. One significant aspect of tumor development is the sensitivity of truncated APC to CtBP oligomerization (46). In colon cancer cases where truncated APC is expressed, the interaction between APC and CtBP is disrupted, leading to the promotion of CRC occurrence and progression (47). CtBP's capacity to induce tumor growth arises from its ability to alter the gene expression patterns of cells, leading to the suppression of genes involved in apoptotic processes, such as Bcl-2 interacting killer, p53 upregulated modulator of apoptosis, NADPH oxidase activator and p53 apoptosis effector related to peripheral myelin protein 22. In addition, it inhibits the activity of tumor suppressors, such as phosphatase and tensin homolog, $p16^{Ink4a}$, $p15^{Ink4b}$ and $p21^{waf1/cip1}$. CtBP also activates the metastasis-associated gene TIAM Rac1 associated GEF 1, facilitating cell migration and invasion (48). Mutations of the APC gene in FAP cases lead to the production of shortened APC proteins that cannot effectively control the activity of the β-catenin transcription factor. Notably, even though CRC cells in FAP cases continue to have the shortened APC protein, it was found that CtBP could facilitate the assembly of these shortened APC proteins by binding to a specific sequence of 15 amino acids that was repeated in the APC protein. Surprisingly, CtBP has the ability to attach itself to the initial, third, or fourth sequence of the 15-amino acid repeats, but it is unable to bind to the second sequence. The formation of CtBP oligomers necessitates the removal of the dimerization region in APC, in addition to CtBP's own dimerization process. A comprehensive examination of APC sequence mutations in individuals with FAP revealed that the truncated APC products consistently favored the initial 15 amino acid repeat sequences (49). Scholars attempted to develop a short hairpin (sh)RNA targeting a particular subtype of APC that is truncated, while preserving the original wild-type APC. They discovered that when they reduced the level of this truncated APC, the transcriptional activity of β-catenin increased in 5 out of 6 CRC cell lines. This demonstrates that the truncated APC is still capable of regulating Wnt signaling by controlling β-catenin levels. Consequently, the truncated APC facilitates the proliferation of CRC cells by moderating β-catenin to a 'suitable' extent (50). Furthermore, scientists have recently identified a selective inhibitor called TASIN-1, targeting APC-truncated cells, while leaving normal human colon epithelial cells and certain cancer cells unaffected, which is quite remarkable. Animal experiments conducted *in vivo* demonstrated that treatment with TASIN-1 effectively hindered the growth of CRC cells with truncated APC, without showing significant toxicity towards CRC cells that had wild-type APC (51). Mizutani *et al* (52) found that a newly developed inhibitor called RK-287107 effectively caused AXIN2 accumulation, suppressed β-catenin expression, reduced TCF/LEF activity, attenuated Myc expression and restrained the growth of CRC cells with APC mutations.

In addition, Novellasdemunt *et al* (53) utilized clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) technology to create different APC truncated isogenic lines and observed that the inhibitory domain of β-catenin (CID) in APC is responsible for determining the pathological levels of Wnt activation and the transformation of tumors. Through a specific mechanism, the depletion of CID in APC truncation leads to the deubiquitination of β-catenin by facilitating the reverse binding of β-transducin repeat-containing protein and ubiquitin specific peptidase 7 (USP7) to the disruption complex. In CRC with APC mutations, the deletion of USP7 effectively suppresses Wnt activation, induces differentiation and hinders xenograft tumor growth by promoting the ubiquitination of β-catenin. Of note, the role of USP7 in Wnt activation is specific to APC mutations, making it a potential therapeutic target specific to CRC.

4. APC truncation and intestinal epithelial cell apoptosis

Contrary to full-length APC, APC mutants exhibit antiapoptotic capabilities through mechanisms that do not involve transcription. TASIN-1, on the other hand, has been found to trigger apoptosis in truncated APC human CRC cells by inducing endoplasmic reticulum stress-related JNK activation, accompanied by the generation of reactive oxygen species. Furthermore, TASIN-1 hampers AKT activity in a cholesterol-dependent fashion. When examining human CRC xenografts in immunodeficient mice, it becomes evident that the molecular mechanism underlying TASIN-1-induced tumor cell death is consistent with what has been observed *in vitro* (54). Multiple studies have demonstrated that APC truncation hinders the process of apoptosis-related caspase cleavage, independent of β-catenin-mediated transcription (55). The introduction of truncated APC, as opposed to full-length APC, provided protection against Sulindac-induced apoptosis in SW480 cells. Conversely, temporarily reducing the levels of APC truncation in SW480 cells led to a decrease in Bcl-2 expression in the mitochondria and an increase in apoptosis (56).

5. APC truncation and intestinal epithelial cell migration

APC exerts control over cell migration through various mechanisms, such as regulating the actin cytoskeleton (57), governing the microtubule network (58) and interacting with APC-stimulated guanine nucleotide-exchange factor (Asef) (59), a specific guanine nucleotide-exchange factor for Rac. A notable observation has been made that the introduction of truncated APC, as opposed to full-length APC, triggers Asef-mediated cell migration in Madin-Darby canine kidney cells. Furthermore, when shRNA was utilized to silence truncated APCs, it noticeably reduced cell migration of SW480 and WiDr cells. However, when shRNA specifically targeted truncated APC, there was no impact on the migration of HCT116 and LS180 cells that had wild-type APC (60). These findings demonstrate that truncated APC, not full-length one, is strong activator of Asef, potentially causing abnormal cell migration in CRC cells. Recent evidence also showed that N-terminal truncation of APC plays a significant role in promoting directed cell migration in various model systems (61). In addition, it was noted that APC, when acting as a kinesin carrier, can be found at the ends of microtubules. This was found in A6 Xenopus epithelial cells, where both full-length APC and APC mutants without the C-terminus could move towards the plus-end of microtubules in a manner dependent on ATP. This movement aligned with the plus-end-directed motility activity was typically associated with kinesin (62). The translocation of APC C-terminal deletion constructs may rely on either heterotrimeric [kinesin family member 3A (KIF3A)/3B/KAP3] or homodimeric (KIF17) kinesin-2, both of which have the capability to interact with the APC-N terminus and facilitate the accumulation of APC at the outer edges of the cell (63,64). The interaction between APC and KIF5 occurs through the C-terminal region and plays a role in stabilizing APC at the end of microtubules, impacting cell migration (65). The presence of the APC C-terminus alone, with or without the Dlg1 binding motif, is capable of correcting the disrupted epithelial cell extrusion direction caused by the expression of APC with a truncated C-terminus. This indicates that the stabilization of microtubules by the APC C-terminus alone is sufficient to restore cell polarity (66).

6. APC truncation and intestinal epithelial cell adhesion

Collective cell remodeling and motility rely on the actin cytoskeleton, exerting a crucial role in the dynamic reorganization of cell contacts. The initiation and growth of actin filaments (F-actin) are facilitated by APC, leading to the enhanced stability and movement of cell junctions. Consequently, APC may contribute significantly to the processes of cellular remodeling and motility. The presence of the APC-dependent actin pool has a crucial role in maintaining appropriate levels of F-actin, E-cadherin and occludin proteins at cell junctions. These proteins are responsible for preserving the length and angle of cell junctions and ensuring the motility and integrity of cellular tips. When the APC protein is truncated, the actin pool is lost, resulting in slower and more random movement of larger cells. This highlights the significance of APC-driven cytoskeletal function in understanding the process of intestinal morphogenesis (57). Epithelial cells possess an exclusive intracellular reservoir of β-catenin, known as *Drosophila* armadillo, serving as a structural element in junctions of adhesion molecules. It is noteworthy that APC proteins potentially participate in the assembly of these adhesion molecules and emerging evidence suggests that APC has a role in facilitating cell adhesion (67). Therefore, the potential function of APC-β-catenin-Armadillo in both Wnt signaling and cell adhesion suggests its possible involvement as a tumor suppressor. It has been suggested that APC mutation truncation could contribute to tumorigenesis by interfering with cell-cell adhesion. Additionally, APC interacts with *Drosophila* armadillo, a specific subset of β-catenin located within cells, to establish a connection between E-cadherin, α-catenin and the actin cytoskeleton (68,69). In animal models with mutant Apc copies, scientists observed a decrease in E-cadherin levels in both intestinal cells and tumor cell membranes. Additionally, the connection between β-catenin and E-cadherin was found to be weakened (70,71). The presence of complete APCs in CRC cells, as opposed to truncated APCs, led to a notable increase in E-cadherin levels on the cell membrane. This resulted in the relocation of β-catenin from the nucleus and cytoplasm to the outer edge of the cell, ultimately enhancing cell adhesion (72,73). Thus, APC may regulate the distribution of β-catenin and E-cadherin between the cytoplasm and the cell membrane in a notable manner, ultimately affecting cell adhesion. A mutant APC that lacks the β-catenin binding domain leads to reduced cell adhesion.

7. APC truncation, DNA repair and CIN

APCs are mainly present within the cytoplasm, while they have the ability to translocate to the nucleus in order to regulate nuclear activities (74). The direct binding between complete APC molecules and polymerase β (Pol-β), flap structure-specific endonuclease 1 (FEN1) and APE1 endonuclease can lead to the prevention of the assembly of base excision repair (BER) proteins on damaged DNA and the hindrance of

long-patch BER (75). The region of APC that inhibits DNA repair, which binds to Pol-β and FEN1, can be found in the N-terminal section and remains present in mutated forms of APC (76). Studies have demonstrated that in cancer cells (e.g., LoVo) expressing truncated APC protein, the assembly of BER proteins is sped up, and APE1, FEN1 and Pol-β are more efficient. However, when full-length APC is reintroduced, FEN1 expression decreases and makes this cell line more responsive to 5-fluorouracil (77). An imbalance in the BER pathway and the potential for CIN and cancer progression may occur as a consequence of heightened APE1 activity (78). Furthermore, APC has the ability to interact with replication protein A32 in order to regulate the response to replication stress (79). In addition, APC plays a direct role in DNA double-strand break repair by being a component of the nuclear complex that contains DNA-dependent protein kinase (80). To sum up, mutations in APC genes can weaken the functions of BER and DSB repair, resulting in the accumulation of genetic changes in CRC cells. As a result, CRC cells with mutant APCs may be more vulnerable to the effects of DNA-damaging chemotherapy drugs (e.g., oxaliplatin and 5-fluorouracil). In addition, APCs have the ability to directly attach to and stabilize microtubules, or indirectly by binding to EB1, a protein found abundantly at the tips of microtubules (81). Of note, scholars also discovered that in cells going through mitosis, APC is localized to kinetochores and forms complexes with BUB1 mitotic checkpoint serine/threonine kinase (Bub1) and Bub3 (82). When APC is depleted in cancer cells, such as U2OS and HCT116, the association between checkpoint proteins Bub1 and BubR1 with kinetochores is reduced, resulting in alterations in the progression of mitosis and an increase in mitotic sliding (83). Consequently, cells carrying the shortened APC gene exhibit a defect in the proper segregation of chromosomes. In addition, when APC and/or EB1 are targeted using small interfering RNA, alignment issues in the mitotic spindle and chromosomes occur. Abnormal spindle structure and weakened attachment of kinetochore microtubules were observed in CRC cells that bear the truncated APC gene (84). Furthermore, the absence of APC led to an elevation in the chromosomal count in mouse hepatocytes (85). To summarize, the presence of APCs with a truncated C-terminus can promote the advancement of CRC by impairing spindle formation and progression during cell division, attributed to the absence of a microtubule-binding domain.

8. Role of APC in CRC

APC plays a pivotal role in CRC by regulating the Wnt/β-catenin signaling pathway, which is critical for maintaining cellular homeostasis and controlling cell proliferation (11,32). Mutations in the APC gene, particularly truncating mutations, result in the loss of functional domains in the APC protein. This typically occurs when truncations remove the C-terminal regions responsible for binding β-catenin, axin and other regulatory proteins, leading to the stabilization and accumulation of β-catenin in the cytoplasm. The accumulated β-catenin translocates to the nucleus, where it activates the transcription of Wnt target genes that promote tumorigenesis (51). For instance, truncations at codon 1,309, one of the most common mutations in FAP and sporadic CRC, result in a premature stop codon. This truncation removes the majority of the C-terminal domains responsible for β-catenin regulation and other cellular processes. Similarly, truncations at codon 1,450 lead to a loss of microtubule-binding domains, which affects APC's role in cytoskeletal dynamics, impairing cell migration and adhesion (38). This structural disruption not only affects β-catenin regulation but also destabilizes APC's interactions with the cytoskeleton, promoting increased metastatic potential. Furthermore, APC mutations are associated with CIN, which is partly driven by the loss of its ability to interact with microtubules, contributing to aneuploidy and tumor heterogeneity (26). Truncations affecting the armadillo repeat and basic domains of APC, crucial for its role in microtubule attachment and spindle formation, contribute to the chromosomal missegregation observed in CRC. The loss of functional domains due to truncating mutations also has implications for the tumor microenvironment, altering the way tumor cells interact with the stroma and immune cells. This disruption can create a microenvironment that supports tumor growth and metastasis (59). Understanding these structure-function relationships in APC truncations is critical for developing more targeted therapeutic approaches in CRC. In this way, novel therapeutic targets may be discovered and strategies may be developed to enhance the efficacy of CRC treatments.

The four most common truncating mutations in APC and their implications in CRC are as follows: The codon 1,309 mutation is found in ~20-30% of CRC cases and causes truncation in the mutation cluster region (MCR), which includes the β-catenin binding and downregulation domains (67). This leads to the stabilization and nuclear accumulation of β-catenin, promoting the transcription of oncogenic target genes, such as c-Myc and cyclin D1. The codon 1,450 mutation, present in ~10-20% of CRC cases, also truncates in the MCR, affecting β-catenin binding sites and Axin interaction domains, resulting in increased β-catenin activity and enhanced tumorigenesis through upregulation of Wnt target genes (69). The codon 1,556 mutation is observed in 5-10% of CRC patients and involves truncation beyond the MCR, affecting additional regions involved in cytoskeletal interactions. This disrupts the role of APC in microtubule stabilization and chromosomal segregation, contributing to CIN and tumor progression (72). Lastly, the codon 1,061 mutation, detected in 5-15% of CRC cases, results in truncation within the armadillo repeats and the MCR, impacting β-catenin and other interaction sites, thereby enhancing Wnt signaling due to defective β-catenin degradation, promoting cell proliferation and survival (81). These mutations are primarily responsible for the disruption of APC's tumor suppressor functions, including its roles in Wnt signaling, cell adhesion, migration and genomic stability, ultimately driving the development and progression of CRC.

9. Summary

The role of APC as a tumor suppressor has long been a significant focus in cancer research. Recently, there has been growing interest in exploring the cancer-causing potential of APC mutants due to emerging evidence. An increasing array of evidence suggested that APC mutants have a noticeable function in the development and advancement of CRC tumors by hindering the tumor suppressor function of APC. As cancer

cells gradually become reliant on the cancer-causing characteristics of truncated APC protein to survive and sustain their malignancy, they experience changes in their signaling network patterns and continuous activation of oncogenes. The utilization of proteomics and the ongoing progress in genome-wide high-throughput screening methods can potentially assist in the identification of novel interaction partners of truncated APCs, contributing to a thorough understanding of the signaling network in CRC cells. While the fundamental role of APC in CRC pathogenesis is well-established, recent research has unveiled new aspects of its function, including its interactions with emerging signaling pathways such as the Hippo, Notch and Hedgehog pathways, and its broader impact on genomic stability. The evolving understanding of APC's role in CRC underscores its remarkable importance in cancer research, highlighting the potential for novel therapeutic approaches and personalized medicine based on APC-related mechanisms. This review consolidated these recent findings, demonstrating that APC plays notable roles in improving CRC diagnosis, treatment and prevention. Acquiring knowledge about how these mutated forms of APC cooperate with downstream effector proteins will be vital in elucidating the molecular mechanisms underlying CRC tumorigenesis, ultimately revealing new targets for drug development and improving targeted therapies for CRC. The evolving understanding of APC's role in CRC underscores its remarkable importance in cancer research, highlighting the potential for novel therapeutic approaches and personalized medicine based on APC-related mechanisms. This review consolidated these recent findings, demonstrating that APC plays notable roles in improving CRC diagnosis, treatment and prevention. The novelties of this review lie in its detailed exploration of APC truncation-specific mechanisms and their unique contributions to CRC progression. In contrast to previous reviews that broadly concentrated on APC mutations, this review highlighted how truncation mutations affect key protein interactions, such as those with AXIN1, β-catenin and the Wnt signaling pathway, leading to profound effects on cellular processes, involving proliferation, migration and adhesion. The review presented novel insights into the 'triple hit' hypothesis, emphasizing the critical role of subsequent genetic alterations following APC truncation in promoting tumor progression. Additionally, the review highlighted emerging findings on the role of CtBP oligomerization in APC truncation, a less explored yet crucial pathway in CRC. Furthermore, the review provided notable perspectives on therapeutic strategies targeting truncated APC, including the development of TASIN-1, which selectively targets APC-mutant cells. It also covered underexplored areas, such as the impact of APC truncation on cytoskeletal interactions, CIN and DNA repair mechanisms, while incorporating recent advancements in experimental techniques (e.g., CRISPR/Cas9). Consequently, these aspects present a comprehensive and updated view of how APC truncation drives CRC, providing new directions for understanding tumorigenesis and potential therapeutic interventions.

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Authors' contributions

TW conceived and designed the study. CF, JF and YH wrote and edited the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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