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Molecular mechanism of adenomatous polyposis coli-induced blockade of base excision repair pathway in colorectal carcinogenesis

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Abstract

Colorectal cancer (CRC) is the third leading cause of death in both men and women in North America. Despite chemotherapeutic efforts, CRC is associated with a high degree of morbidity and mortality. Thus, to develop effective treatment strategies for CRC, one needs knowledge of the pathogenesis of cancer development and cancer resistance. It is suggested that colonic tumors or cell lines harbor truncated adenomatous polyposis coli (APC) without DNA repair inhibitory (DRI)-domain. It is also thought that the product of the *APC* gene can modulate base excision repair (BER) pathway through an interaction with Pol- β and flap endonuclease 1 (Fen-1) to mediate CRC cell apoptosis. The proposed therapy with temozolomide (TMZ) exploits this particular pathway; however, a high percentage of colorectal tumors continue to develop resistance to chemotherapy due to mismatch repair (MMR)-deficiency. In the present communication, we have comprehensively reviewed a critical issue that has not been addressed previously: a novel mechanism by which APC-induced blockage of single nucleotide (SN)- and long-patch (LP)-BER play role in DNA-alkylation damage-induced colorectal carcinogenesis.

Graphical Abstract

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Conflict of interest

The authors declare that there is no conflict of interest.

Role of APC in DNA repair, carcinogenesis and therapeutics

Keywords

Adenomatous polyposis coli; base excision repair; DNA damage; colorectal carcinogenesis

Introduction

Colorectal cancer (CRC) is the third most common cause of cancer-related death in both men and women in the Western hemisphere. In 2015, the American Cancer Society estimated that 132,700 new CRCs (93,000 colon and 39,610 rectal cancers) would be diagnosed and that 49,700 deaths would occur with this disease in the United States [1]. Prognosis and therapy depends on the stage of the tumor at the time of diagnosis. Therapeutic interventions include surgery, chemotherapy and/or radiation. Of the three modalities, surgery appears to be the most effective treatment for early stages that have adequate surgical margins with no invasive characteristics. Chemotherapy and/or radiation are often an adjunctive therapy for stages II and III of CRC patients; however, such therapy is less effective due to high rates (nearly 30–50%) of recurrence and/or drug resistance [2–4]. To understand why CRC is associated with high recurrence and drug resistance rates, one needs a better understanding of CRC pathogenesis.

CRC develops through a series of histologically distinct stages from “adenoma to carcinoma” [5] and follows a temporal order in which genetic mutations and epigenetic events occurring in different genes generate multiple pathways for CRC progression [6–9]. One of the earliest events during this multistep process of tumorigenesis in CRC stems arises from mutations in the *APC* gene [10–13]. In mice that carry the targeted conditional mutation of *Apc*, the development of CRC from the loss of APC function has been observed [14]. Additionally, *Apc* knockout demonstrates a DNA damage signature and genomic instability in the liver that is further enhanced with loss of p53 [15]. However, the role of wild-type APC in response to carcinogen-induced DNA damage in colorectal carcinogenesis is not clear.

The focus of this review article is to highlight the important role of wild-type and mutant APC in the repair of abasic DNA by the BER pathway, and the potential link between BER and colorectal carcinogenesis. We will focus primarily on the following critical aims that have not been previously described before: (i) Understand the link between APC and BER, (ii) Determine the factors that may affect the cellular consequences (transformation vs. apoptosis) of the APC block of BER, (iii) Understand the mechanisms by which APC/BER interaction influences CRC carcinogenesis and (iv) Determine whether the APC/BER pathway interaction may be an alternative chemotherapeutic target.

APC gene and mutation in CRC

The *APC* gene product is a 310-kDa-homodimeric protein, which is localized in both the cytoplasm and nucleus [16–21]. It is expressed constitutively within the normal colonic epithelium. At the cellular level, wild-type APC is critical for cytoskeletal integrity [17, 22], cellular adhesion [23, 24], cell migration [21, 25], and Wingless/Wnt signaling [26–28]. In addition, it can act to suppress tumor growth through several different mechanisms. Wild-type APC binds to EB1 and DLG (a tumor suppressor protein) to regulate microtubule polymerization [29–32] and cell cycle progression from G₀/G₁ to S phase [33], respectively. APC may also act as a negative regulator of β -catenin signaling in the transformation of colonic epithelial cells [34, 35]. The β -catenin/Tcf4 complex regulates the proto-oncogene and cell cycle regulator *c-myc* [36], the G₁/S-regulating *cyclin D1* [37], the gene encoding the matrix-degrading metalloproteinase, *matrilysin* [38], the AP-1 transcription factors *c-jun* and *fra-1*, and the urokinase-type plasminogen activator receptor gene, *uPAR* [39]. The β -catenin/Tcf4 complex-mediated expression of *c-myc* regulates the expression of *Cdk4* and links the *APC* mutation to β -catenin stabilization, *c-myc* upregulation and abrogation of Cdk4-mediated G1/S transition [40, 41]. Furthermore, *c-myc* deletion has been shown to rescue *Apc* deficiency in the small intestine of mice [42, 43].

In colorectal tumorigenesis, mutations of the *APC*, *Ki-ras*, deleted in colorectal cancer (*DCC*), and *p53* genes play important roles at different stages of colorectal cancer development [26, 27]. About 60 to 80% of sporadic colorectal cancers and adenomas have mutations in the *APC* gene [8, 10, 12]. Mutation of the *APC* gene is an early event in familial adenomatous polyposis (FAP), a syndrome in which there is an inherited predisposition to colon cancer [10, 11]. An association has also been shown between FAP and germline mutations in the mutation cluster region (MCR) of APC [44–47]. A truncation mutation involving the MCR is thought to be necessary for the loss of β -catenin binding and nuclear localization signals in APC that promotes tumor progression [10, 26, 48–50]. A recent study has shown that animals with homozygous truncating mutations at codon 1638 of *APC* do not develop tumors and survive through adulthood [51]. Patients with mutations outside of the MCR region may exhibit a milder phenotype in CRC development [52–54]. Thus, it is now well established that mutations in *APC* may be necessary for the early onset of polyposis.

Base excision repair (BER) in CRC

The damage to genomic DNA base-pairs can occur by both exogenous and endogenous mutagenic agents. It has been estimated that approximately 10^6 abasic sites are generated per mammalian cell per day [55]. Abasic sites are unstable and degrade spontaneously into DNA-strand breaks by β -elimination and are also highly mutagenic due to creation of non-template DNA and RNA synthesis. Despite the large number of abasic sites generated by each cell per day, the number of mutations is extremely low. This is because most of the damaged DNA bases can be efficiently repaired by several DNA repair systems [56]. However, deficiencies in the DNA repair pathways results in unrepaired damaged DNA bases, which are thought to be a major source of intermediate precursors for carcinogenesis and tumorigenesis [57].

In humans, deficiency in DNA repair has been linked to a number of genetic diseases characterized by radiation sensitivity and cancer-prone syndromes [58]. It is proposed that about 15% of hereditary nonpolyposis colon cancers (HNPCC) have defects in one or more proteins in the DNA mismatch repair (MMR) pathway. A significant concordance between the *in vitro* replication errors of Pol- β and *in vivo* point mutations of the *APC* gene has been suggested as a leading cause of CRC [59]. Most DNA repair mechanisms involve the participation of enzymes and other proteins that recognize structural alterations in DNA [60–63].

In mammalian cells, BER can proceed through at least two pathways designated as the “single nucleotide (SN)-BER” and “multi-nucleotide or long-patch (LP)-BER” pathways (Fig. 1). These two pathways are differentiated by the repair patch size, as well as, by the contribution of different proteins to the pathway [64–66]. In both pathways, repair is first initiated by the recognition and removal of the modified base by a DNA glycosylase. The two types of DNA glycosylases – monofunctional and bifunctional – generate an abasic site (AP). Monofunctional DNA glycosylases cleave only the glycosidic bond between N and C1. This cleavage protects the abasic site until apurinic/apyrimidinic (AP) endonuclease 1 (APE-1) cleaves the DNA backbone at the 5'-end of the AP-site. The bifunctional DNA glycosylases have an additional AP-lyase activity between the sugar and the base to establish an abasic-site [67]. At the latter DNA cleavage site, APE-1 generates a 3'-OH and 5'-deoxyribose phosphate (5'-dRP) ends [68–70]. Second, the remaining 5'-dRP residue is cleaved by a 5'-deoxyribose phosphate lyase (dRP-lyase) activity of Pol- β to yield a 5'-phosphorylated gapped-DNA strand. Third, Pol- β incorporates the correct base at the site of the damaged base with its polymerizing activity. Lastly, the DNA ligase-I or III seals the nick [71]. This multi-step repair process becomes more complicated once the AP-site becomes oxidized or reduced and cannot undergo the dRP-lyase activity of Pol- β . Under these circumstances, the repair of DNA is accomplished through LP-BER. The Pol- β -dependent strand-displacement synthesis generates a longer repair patch and a 5'-overhang of a single-stranded DNA-flap with a modified sugar at its 5'-end. The 5'-overhang DNA-flap is cleaved by flap endonuclease 1 (Fen-1), and finally the nick is sealed by DNA ligase I or III [56, 65, 72–76].

The regulation of the SN- and LP-BER pathways becomes more complex when accessory proteins interact directly with one or more of the BER proteins and alter their activity. For example, Werner's syndrome protein [77, 78], poly(ADP-ribose)polymerase-1 [79, 80], proliferating cell nuclear antigen [64, 81–83], p53 [84], replication protein A [85], X-ray cross-complementing group 1 (XRCC1) [86], and arginine methyltransferase 6 (PRMT-6) [66] function as accessory proteins in the BER pathway. Our studies suggest that APC is another accessory protein that interacts with Pol- β and Fen-1 and blocks SN- and LP-BER activities [68, 87–89]. Since Arg83 of Pol- β is one of the amino acids involved in the interaction with APC, it would be interesting to determine whether the methylation of Pol- β at this residue affects APC-binding and its function.

APC/BER interaction and CRC carcinogenesis

The APC block of BER in response to exposure to DNA-alkylation damage can result in the transformation of colonic epithelial cells. This has also been shown in cigarette smoke carcinogen-induced neoplastic transformation of normal breast epithelial cells both *in vitro* and *in vivo* models [90–92]. The role of APC in BER is based upon the finding of PCNA-interacting protein (PIP)-like box Qxx(h)xx(aa) in APC (amino acids Gln1256, Ile1259 and Tyr1262) [68]. Using site-directed mutagenesis, the APC amino acid residues Ile1259 and Tyr1262 are important for the interaction and functional activity of Pol- β ; this interacting domain of APC is known as the DNA repair inhibitory (DRI)-domain [87]. The DRI-domain of APC is located in the N-terminal region and is spared by mutations of MCR-associated truncation, which compromises the function of APC and contributes to chromosomal instability [93, 94] (Fig. 2). In a series of reconstituted or cell-based *in vitro* experiments, APC blocks Pol- β -directed LP-BER and SN-BER by blocking the dRP-lyase and strand-displacement activities of Pol- β [54, 68, 87, 89].

Although, APC is present in the purified BER complex assembled onto the basic DNA substrate [95], it is not clear whether APC directly interacts with the abasic DNA, is recruited by or recruits BER proteins. In recent studies, a direct interaction of APC with DNA has been shown [96, 97]. The DNA binding activity of APC has been implicated in the blockade of DNA replication, S phase progression, and drug-induced apoptosis [98, 99]. In mouse embryonic fibroblast cells, MMS-induced levels of APC block LP-BER and increase apoptosis [88]. Our recent findings [100–103] indicate that the wild-type APC can induce sensitivity of DNA-alkylating drugs to CRC cells by blocking the BER pathway (Fig. 3). On the other hand, mutations in the APC gene can cause resistance of DNA-alkylating drugs to CRC cells by removing its interference with the BER pathway. This view has been supported by subsequent studies showing that mutations in the APC gene influences 5-fluorouracil (5-FU) resistance to CRCs [99, 104].

APC/BER in determining transformation versus apoptosis

The precise relationship between the extent of DNA damage, duration of DNA damage, DNA repair capacity of the cell, and the role of APC in colorectal carcinogenesis is not well-established. The current understanding suggests that when a threshold limit of DNA damage is incurred, the cell tries to repair the damage; however, a few cells may escape the repair,

acquire additional cell survival characteristics, and become tumorigenic. When the extent of DNA damage sustained is higher than the repair capacity, the cell becomes apoptotic [105–107]. Hence, the risk for the development of cancer is based on the inter-individual variation in carcinogen metabolism, amount of carcinogen-DNA adducts and DNA repair capacity of the cell [108, 109].

Molecules that regulate cellular proliferation and transformation include APC, claudin-1, and azoxymethane (AOM) amongst many others. Previous studies show that APC regulates cellular proliferation and transformation induced by the activation of RAS and β -catenin signaling pathways and/or cooperated by other genes, such as *Dnah3*, *Ahnak*, *Stk17b*, and *Rbm9* [110, 111]. Claudin-1 overexpression enhances intestinal epithelial cell susceptibility to APC-mediated colon tumorigenesis [112]. The carcinogen AOM causes transformation of normal colonic epithelial cells in culture and animal models in a dose- and duration-dependent manner [113]. AOM-induced transformation and survival or apoptosis of rat colonic epithelial cells is measured by the level and repair of ⁶O-methyl guanine adducts in DNA [114, 115]. In AOM-induced mouse colon tumors, the development of colon cancer is thought to be associated with loss of wild-type APC protein and by mutations in the *Apc* gene that alters its expression [116, 117]. Later, mutations in *Apc* gene were determined in AOM-induced colorectal carcinogenesis in rats [117]. However, the precise relationship between the extents of DNA damage, the duration of DNA damage, the DNA repair capacity of the cell, and the role of APC in colorectal carcinogenesis is not well-understood. Therefore, it is imperative to define the mechanism(s) that may explain whether the cells harboring wild-type APC that sustain DNA damage survive, enter the carcinogenesis cascade, or become apoptotic.

APC/BER interaction as a chemotherapeutic target

DNA-alkylating agents are commonly used in the treatment of brain tumors, ovarian cancer, malignant melanomas, and various hematological tumors [118–120]. These agents have either one or two reactive groups that interact covalently with nucleophilic centers in DNA. Such reactive sites are present in all four bases, and are attacked with different affinities and specificities. The most reactive sites are the ring nitrogen atoms (N⁷ of guanine (N⁷mG) and N³ of adenine (N³mA)) and under normal circumstances they are repaired by the BER pathway [121, 122]. Alkylation also occurs at the nucleophilic oxygen sites, such as the O⁶ position of guanine (O⁶mG), which is repaired by O⁶-guanine DNA methyltransferase (MGMT) [123–125] or mismatch repair (MMR) pathways [126–128]. N⁷mG and N³mA are most frequently methylated adducts comprising 80–85% and 8–18% of total DNA methylated adducts, respectively. N³mA adducts are readily hydrolyzed, while N⁷mG adducts are stable for longer times with an *in vitro* half-life of 40–80 hours [129]. The O⁶mG are approximately 8% of the total methylated DNA adducts, and they are more stable and persist longer in DNA in the absence of MGMT [123]. The inappropriate pairing of O⁶mG lesions during DNA replication causes pre-mutagenic and pre-toxic GC to AT transitions [130]. On the other hand, although N⁷MeG and N³MeA lesions do not result in mismatch, they do have indirect genetic consequences through secondary lesions of abasic sites [131–134]. Unrepaired abasic sites hinder DNA replication and give rise to base pair substitutions including GC to AT transitions and AT to TA and GC to TA transversions

[131, 134–136]. Thus, N⁷MeG and N³MeA lesions, while less mutagenic than O⁶MeG lesions, are effective in stimulating the recombinational change that leads to genetic duplications. Since N⁷MeG and N³MeA lesions are repaired by BER, it is clear that the BER pathway is critical for determining DNA alkylation-induced carcinogenesis. Any defect in the BER pathway that causes an accumulation of these lesions can also produce cytotoxicity, a fact that has been exploited as a chemotherapeutic target for cancer cell death [118–122, 137–139].

Regardless the attempts to improve patient outcomes by incorporating new active systemic agents into clinical practice, there has been little improvement in the metastatic CRC patient cure rate. In spite of the best practice of 5-FU with or without additional therapy to eradicate micrometastatic disease after “curative” surgery for early stage CRC or in those with oligometastatic disease, most cancers relapse within the first few years following treatment completion. This indicates a relatively rapid repopulation of neoplastic progeny, i.e., CRC stem cells [140, 141]. Treatment with higher or prolonged doses of multiple drug combinations, such as 5-FU and oxaliplatin, compromises the patient’s quality of life and leads to serious side-effects [142, 143]. Despite decades of use, a thorough understanding of the mechanisms of action of 5-FU and interventions to overcome resistance are still relatively limited. Thus, there is critical need for a rational design of mechanism-based systemic therapy with well-characterized, specific targets [144, 145]. The efficacy of many chemotherapeutic drugs, such as 5-FU and oxaliplatin can be improved by blocking specific DNA repair pathways. Since multiple pathways are involved in the repair of 5-FU and oxaliplatin-induced DNA lesions, multiple inhibitors will be required to achieve the desired goal. Therefore, we propose that targeting one specific pathway, such as Pol-β and using the therapeutic drug, such as TMZ, may prove to be a good future strategy for significantly improved outcome for patients with colorectal cancer.

Numerous Pol-β inhibitors, with limited success that have been reported in recent years, are summarized in Table 1 [100–102, 146–164]. Despite the number of available drugs, more potent and selective inhibitors of DNA Pol-β are still needed. A new and emerging concept is to sensitize cancer cells to DNA-damaging agents by inhibiting various proteins in the DNA repair pathways [138]. Small chemical compounds have been identified by molecular docking or NMR studies to target the BER pathway by inhibiting AP endonuclease 1 (APE1) and Pol-β activities [153, 165]. For Pol-β, the most active compound identified by NMR chemical shift mapping is pamoic acid [153]. However, this compound, which inhibits dRP-lyase activity, blocks only SN-BER of Pol-β, and achievement of this block requires administration of a high concentration of the reagent. Since abasic DNA damage can also be repaired by LP-BER, there is a need for agents that can block both Pol-β-directed SN- and LP-BER pathways.

Taking the advantage that APC interacts with Pol-β and Fen1, blocks both SN- and LP-BER pathways [54, 68, 87–90, 92], and interacts with amino acid residues Thr79, Lys81 and Arg83 of Pol-β [89], specific potent small molecule inhibitors (SMIs) targeting APC have been identified by molecular docking. The SMIs can enhance the efficacy of the current chemotherapeutic drug TMZ to reduce the growth of colon cancer cells both *in vitro* and *in vivo* [100–102]. Based upon these studies, we have suggested the role of APC in cancer cells

and a novel site for the development of therapeutic drugs. This idea has been further supported by other laboratories [99, 104, 166–168].

Conclusion

Overall this review establishes, for the first time, the involvement of APC in DNA damage-induced carcinogenesis and how the DNA damage strategy can be used for APC-mediated apoptosis of colon cancer cells. The small molecular inhibitors mimic the interaction of APC with Pol- β and block Pol- β -directed BER and increase the sensitivity of TMZ in both MMR-proficient and MMR-deficient colorectal tumors. This is an important asset for the SMI because it can bypass the colorectal cancer resistance due to MMR-deficiency. Further studies are needed to understand how the interaction of APC or small molecular weight inhibitors may improve the use of TMZ and other drugs to modulate the antitumor activity of the targeted cell without affecting the normal cell. These studies will help to advance the field of colorectal carcinogenesis.

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Abbreviations

AOM	azoxymethane
AP	apurinic/apyrimidinic
APC	adenomatous polyposis coli
APE1	apurinic/apyrimidinic endonuclease
BER	base excision repair
DRI	DNA repair-inhibitory
dRP	2'-deoxyribose 5'-phosphate
LP	long-patch
MCR	mutation cluster region
Pol-β	DNA polymerase β
SN	single nucleotide
TMZ	temozolomide

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Figure 1. Model of BER pathway

DNA repair of abasic sites diverge after the generation of the 3'-hydroxyl group. The SN- or LP-BER pathways and their known protein components are summarized. The interaction of APC with BER pathway is also depicted.

A. Structure of APC with DRI-domain

B. Structure of Pol-β with APC interaction site

Figure 2. Structures of APC and Pol-β

Panel A, the 2843 amino acid sequence displays an armadillo domain near the N-terminus. There are two β-catenin binding domains. The first 15-amino acid repeat can bind β-catenin, but its functional significance is still obscure, while the 20-amino acid repeat can bind β-catenin with a high affinity upon phosphorylation. The DRI-domain (showing the Pol-β interacting amino acids Ile1259 and Tyr1264), just upstream of MCR, is involved in the regulation of the BER pathway. Asef, APC-stimulated guanine nucleotide exchange factor; DLG, Drosophila discs large; EB1, end-binding protein 1, KAP3A, kinesin superfamily-associated protein 3A; NES, nuclear export signal; NLS, nuclear localization signal; PP2-B56α, protein phosphatase 2A B56α subunit. **Panel B**, depicts the crystal structure of Pol-β that shows the APC interacting amino acids Thr79, Lys81 and Arg83.

Figure 3.
A hypothetical model for the role of APC blockade of BER in carcinogenesis and chemotherapy.

Table 1Summary of the Pol- β inhibitors.

	Inhibitors	Activity	Reference
1	Thymidine 5'-monophosphate analogs	Irreversible inhibitor of the lyase activity	146
2	Dideoxythymidine triphosphate (ddTTP)	Polymerase activity	147
3	Nigranoic acid	Polymerase activity	148
4	Suramin	Polymerase activity	149
5	Fatty acids	Competing with both the substrate- and template-primer binding	150
6	Koetjapic acid	Competing with both the substrate- and template-primer binding	151
7	D-mandelonitrile-beta-D-glucoside	Competing with both the substrate- and template-primer binding	152
8	Pamoic acid	Binds with 8 kDa domain	153, 164
9	Fomitelic acids	Polymerase activity	154
10	Lithocholic acid	Competitive inhibition with substrate and non-competitive inhibition with template-primer	155
11	3,4,5-Tri- <i>O</i> -galloylquinic acid	Competing with template-primer binding	156
12	Sulfated glycolglycerolipids	Competitive inhibition with template-primer and non-competitive inhibition with the substrate	157
13	Biscoumarin and sterols	Inhibitor of the lyase activity	158, 159
14	Sesquiterpenoids and triterpenoids	Inhibitor of the lyase activity	160, 161
15	Rhodamine-based small molecules	Inhibits polymerization and TdT activity	162, 163
16	NSC124854	Inhibitor of the lyase and strand-displacement activities	100
17	NSC666715	Inhibitor of the lyase and strand-displacement activities	101, 102