Role of adenomatous polyposis coli (APC) gene mutations in the pathogenesis of colorectal cancer; current status and perspectives

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1. Introduction

Colorectal cancer (CRC) is the third most common cancer and the fourth most common cause of cancer-related deaths (about 8.5% of total cancer deaths) worldwide [1,2]. In most parts of the world, the incidence of new CRC cases in men is greater than for women (10.0% versus 9.2% of cases, respectively) [3]. There are several factors that may account for these gender differences in CRC. Women are believed to better engage in CRC screening than men. There are thought to be protective effects of female sex steroid hormones and different responses to carcinogens between genders that may also account for gender differences in the incidence of CRC [4]. It is anticipated that by 2030, there will be more than 2.2 million new CRC cases and 1.1 million deaths resulting from CRC, globally [5].

CRC develops through a process called the adenocarcinoma sequence, initiating via the transformation of the normal colonic epithelium of inner walls of the large intestine to a small, non-cancerous (benign) tumors called adenomatous polyps, which ultimately lead to adenocarcinoma [6]. The genetic basis of CRC is complicated and heterogeneous, and include various somatic and germline gene mutations, such as point mutations, aberrant gene fusion, deletion or insertion, and epigenetic alternations [7].

The majority (70–80%) of CRCs occur sporadically [8]. Sporadic CRC is much more common in old age (70–75 years old) without a genetic predisposition or a positive family history. It is believed that the great proportion of sporadic CRC tumors carry somatic mutations in both the adenomatous polyposis coli (APC) alleles in the early stages of CRC [9,10]. However, around 20% of CRC patients have familial aggregation (that is they are a hereditary form), demonstrating a family history of CRC in at least one other relative [11].

The genetic basis of the hereditary forms of CRC is not well defined. The hereditary types of CRC can be divided into polyposis and non-polyposis syndromes [12]. The most common form of hereditary non-polyposis syndromes is HNPCC, also known as Lynch syndrome, accounting for approximately 2%–3% of all CRCs [11]. 30%–60% of HNPCC patients possess germline mutations in DNA mismatch repair genes such as MLH1, MSH2, MSH6, and PMS2 which lead to microsatellite instability (MSI) phenotype of tumors (Fig. 1) [11]. In addition, there is some evidence that mutations in the DNA mismatch repair system might lead to somatic APC mutations in a small proportion of HNPCC patients. This could be due to the accumulated alterations in APC coding regions and/or widespread instability in microsatellite sequences. In fact, some HNPCC tumors may harbor APC mutation because of mutations in the DNA mismatch repair system in the later stages of CRC [13,14].

On the other hand, familial adenomatous polyposis (FAP) is the most common and best recognized hereditary polyposis syndrome. The incidence of FAP accounts for 0.5%–1% of all CRCs [12]. Most cases of FAP are due to germ-line mutations in the APC gene, resulting in a chromosomal instability (CIN) phenotype of tumors (Fig. 1) [15]. Based on the age of onset of the disease and the number of colorectal Adenomatous polyps, FAP, is divided into two classes: 1) the classical FAP (CFAP) in which the average age of developing a tumor is 39 years and patients develop thousands of Adenomatous polyps in the colorectal region with 100% lifetime risk for developing to invasive carcinoma [16], and 2) attenuated FAP (AFAP, also called attenuated Adenomatous Polyposis Coli or AAPC) which the occurrence of colonic adenomas are <100 and average age of onset is >40 [17,18].

APC protein is a component of the Wnt signaling pathway [19]. Wnt signaling is classified into two different pathways: the canonical and non-canonical pathways [20]. APC protein is a tumor suppressor, and has a functional role in the canonical (β-catenin-dependent) Wnt signaling pathways [21]. Moreover, APC can inhibit the initiation and development of colorectal tumor, independently of canonical Wnt signaling. APC assists in chromosome segregation, establishes cellular polarity and migration, and represses DNA replication [22]. It has been shown that during the early stages of non-hypermethylated CRC development, a high portion (~80%) of CRC tumors harbor somatic inactivating mutations in the APC gene [23–26]. APC mutations contribute in early adenoma creation leading to chromosomal instability by triggering spindle abnormalities and deregulation of microtubules/actin cytoskeleton. Moreover, APC mutations increase cell migration by reducing cell adhesion via deregulation of β-catenin and E-cadherin distributions among the cytoplasm and the cell membrane [27,28]. Xu et al. demonstrated that over-expression of erythropoietin-producing hepatocyte (EphB6), a member of the tyrosine kinase family,
along with APC gene mutations, increases proliferation, migration, and invasion in colon epithelial cell line, IMCE, supporting the role of APC mutations in promoting tumorigenesis in CRC [29]. Furthermore, recent findings have highlighted the clinical application of the APC gene analysis in CRC diagnosis, prognosis and appropriate therapeutic intervention [30]. Therefore, a better description and classification of APC gene mutations would be useful for CRC prevention and treatment. Here we summarize the role of APC mutations in the initiation and progression of CRC. We will also discuss the diagnostic and prognostic value of APC in the pathogenesis of CRC for better development of personalized medicine in CRC patients.

1.1. Canonical Wnt/β-catenin signaling pathway

In the absence of Wnt proteins, β-catenin is recruited by the destruction complex. The destruction complex is composed of Axis inhibition protein (Axin), casein kinase 1 alpha (CK1α), Glycogen synthase kinase 3 beta (GSK3β) and APC [31]. In this complex, β-catenin initially becomes phosphorylated at the N-terminal end by CK1α at serine residue 45. This phosphorylation enables GSK3β to phosphorylate β-catenin at serine/threonine residues Ser-33, Ser-37, and Thr-41. Next, β-catenin is ubiquitinated by a member of the F-box protein family, beta-transducin repeat domain containing E3 ubiquitin protein ligase (β-TrCP), leading to β-catenin destruction in the proteasome complex and suppression of β-catenin-mediated expression of Wnt target genes in cells [32]. APC and Axin are two scaffold proteins in this complex that coordinate these phosphorylation processes by facilitating the assembly of the multiprotein destruction complex. Because both APC and Axin have binding sites for β-catenin, they recruit β-catenin to the destruction complex, allowing CK1α and GSK3β to phosphorylate β-catenin. As a result, any alteration in these two scaffolding proteins leads to dissociation of the destruction complex, followed by inhibiting the degradation of β-catenin [33].

However, upon binding to the complex of frizzled (FZD) receptor, Wnt proteins, a seven transmembrane G-protein coupled receptor, and its co-receptors, low-density lipoprotein receptor-related proteins 5/6 (LRP5 or LRP6), triggers the Wnt signaling pathway [34]. As a result, a phosphorylated adaptor protein, disheveled (Dvl), binds to the FZD receptor and promotes the aggregation of FZD/LRP complexes in the plasma membrane. Then, the active pathway dissociates the destruction complex and prevents β-catenin from phosphorylation and degradation, by recruitment of Axin scaffold protein, to the disheveled in the cell membrane. Next, the accumulated intact β-catenin is transferred to the nucleus, and there interacts with members of T cell factor (TCF)/lymphoid enhancer factor (LEF) family of transcription factors and increase the expression of Wnt target genes to regulate different cellular processes including proliferation, adhesion, differentiation, and migration. Deregression of these β-catenin-mediated functions leads to increasing migration and proliferation of cells, decreasing of cellular adhesion and induction of metastasis in CRC patients [24].

1.1.1. The role of APC in the canonical Wnt pathway

The anti-oncogenic role of APC, including its regulation of Wnt signaling is mediated by both cytoplasmic and nuclear mechanisms. APC is an essential component of the cytoplasmic destruction complex, inducing the proteolytic degradation of β-catenin [22]. In different Wnt-on and Wnt-off situation, Axin acts in two distinct phosphorylation states in the “signalosome” and destruction complex, respectively. It has been reported that there is a dependency of Axin phosphorylation sites to APC in either Wnt-stimulated or unstimulated states. In addition to APC’s function in the destruction complex, it’s role is highlighted for the rapid transition in Axin followed by Wnt stimulation, and for the association of Axin and Wnt co-receptor LRP6/Arrow [35]. Furthermore, Saito-Diaz et al. have reported that independent of Wnt ligand, Wnt receptor suppression can inhibit the pathway in APC-deficient cells. Hence, APC is capable of inhibiting Wnt signaling activity by preventing activation/internalization of Wnt receptors and also by blocking the formation of ligand-independent and clathrin-dependent “signalosome” in Drosophila as well as mammalian cells [36].

The interaction of APC nuclear fraction with chromatin-associated β-catenin at Wnt-activated target genes including Axin2, DKK1, MYC and SPS, is accompanied by a transcriptional co-repressor C-terminal binding protein (CTBP) and inhibition of Wnt signaling in CRC cells. Following this temporary interaction, β-catenin is removed, and co-repressors such as HDAC and TLE-1 inhibit the transcription process [22].

1.2. Mutation in Wnt signaling components

The Wnt/β-catenin cascade has emerged as a highly conserved growth-control signaling pathway and contributes to the morphogenesis and maintenance of tissue homeostasis [37]. As a result, any alteration in the principal elements of this pathway leading to hyper-activation and leads to the initiation and progression of many types of cancers, including CRC [38]. Axin1 and β-catenin mutations are two well-defined carcinogenic features that are associated with hyperactivity of the Wnt/β-catenin signaling cascade during CRC development. The role and prevalence of Axin and β-catenin mutations in colorectal cancer has been summarized in reviews by Webster et al. and Yang et al., respectively [39,40]. Briefly, Axin1, one of the key elements of the Wnt/β-catenin pathway, is in direct association with other components of the destruction complex and because it is the least abundant component, accounts for a rate-limiting factor of this complex. Therefore, Axin1 inactivating mutations result in aberrant activation of Wnt/β-catenin signaling. The Axin1 tumor suppressor gene is located on chromosome 16p13.3 and consist of 10 exons. Most of the Axin1 gene mutations in CRC occur in exons 1, 2, 3, 4, 5 and 10, where the APC (exon1, RGS domain), Mitogen-Activated Protein/Extracellular Regulated Kinase Kinase (MEKK), GSK3β (exon 3 and 4), β-catenin (exon5) and DVL (exon 10) binding domains are located [41].

β-catenin has a bi-functional role in cell-adhesion and also in gene transcription as a downstream target of the canonical Wnt pathway [42]. β-catenin target genes are involved in various cancer-related signaling pathways such as proliferation, differentiation, apoptosis, survival, migration, and angiogenesis [43]. β-catenin is encoded by CTNNB1 gene that is located at 3p22.1. The vast majority of CRC-associated β-catenin mutations that lead to Wnt hyper-activation are found in exon 3 of the gene. Exon 3 encodes the NH2-terminal regulatory domain of β-catenin, which is necessary for phosphorylation by CK1α and GSK3β serine/threonine kinases in the destruction complex [44,45]. Wnt ligand-responsive cells can be regulated by another negative feedback mechanism consisting of the cell surface transmembrane E3 ubiquitin ligase Zinc and Ring Finger 3 (ZNRF3) and its homolog ring finger protein 43 (RNF43). RNF43/ZNRF3 ubiquitinate frizzled, leading to its degradation. R-spondin proteins (RSPO) links leucine-rich-repeats-containing G-protein-coupled receptor and RNF43/ZNRF3, preventing the ubiquitination of frizzled [46]. Giannakis et al. have demonstrated that somatic mutations of RNF43 have emerged in more than 18% of colorectal adenocarcinomas and endometrial carcinomas [47]. In addition, some functional fusion genes such as protein tyrosine phosphatase receptor type K with
2. The role of APC mutations in the pathogenesis of CRC

Mammalian cells carry two distinct APC genes, APC and APC2 (APCL). APC2 is highly expressed in the brain and is involved in central nervous system development. Moreover, APC2 is highly conserved among different species and has a similar structure to APC. Therefore, APC and APC2 might lead to functional genetic redundancy in the Wnt signaling pathway. APC and APC2 proteins share a common domain consisting of several 20-amino acid repeats (20AARs), which binds to the β-catenin within the destruction complex. Hence, APC2 can also participate in the destruction complex and inhibit β-catenin activity.

The APC gene is located on chromosome 5q21–22 and comprises 15 coding and 3 noncoding exons that encodes a large protein (2843 amino acid, 8529 coding bp) with several functional domains. This multifunctional protein is expressed in many tissues including crypts and the luminal surface of adult colon tissues [49]. Loss of APC function leading to Wnt/β-catenin signaling hyper-activation is considered as one of the main driving forces of CRC tumorigenesis [27]. However, in contrast to APC2, APC has 15-amino acid repeats (15AARs) motifs, which confer a higher β-catenin binding affinity for APC. As a result, although APC2 may inhibit over-activation of Wnt signaling, it does not suppress Wnt signaling as efficiently as APC does [28,50]. Li et al. demonstrated that destruction complex remains intact in cells containing truncated forms of APC. They suggested that in CRCs, APC truncations induce Wnt/β-catenin signaling by inhibition of β-catenin ubiquitination within the destruction complex, although the exact molecular mechanism is still ambiguous [51]. Furthermore, Yang et al. showed that β-catenin is phosphorylated in degradation complex, but APC mutants cannot release phosphorylated β-catenin from the complex and therefore prevents the proper assembly of the ubiquitin ligase complex in CRC cells [52].

2.1. Somatic APC mutations

Approximately 80% of all sporadic non-hypermutated CRC patients carry APC somatic mutations (Fig. 1) [53]. Mutations of both APC alleles and loss of APC gene function is the first step for malignant transformation in sporadic CRCs [9]. These mutations can be detected in small adenomas at the earliest stage of neoplasia and stay at a stable level as the tumor develops from adenoma to carcinoma [54]. Recent studies have demonstrated that somatic APC mutations are enriched in a specific area of the APC gene (exon 15) called the mutation cluster region (MCR) which spans codons 1285 and 1580 [17]. Some of these mutations are small insertions, deletions and point mutations that lead to truncated proteins. In fact, only 8% of the whole coding region of the APC gene, MCR, is responsible for 80% of all somatic mutations in CRC [17]. Furthermore, there are three mutational hotspots for somatic mutations which occur at codons 1309, 1450 and 1554 corresponding to nearly 7%, 8% and 5% of all somatic mutations respectively (Fig. 2) [17].

To further investigate the frequency of APC mutations in CRC patients, Jauhri et al. studied several mutations in the six potential CRC biomarker genes including KRAS, BRAF, PIK3CA, NRAS, TP53, and APC. They proved that APC mutations had a significant association with the T2 stage of tumor growth. Moreover, 39 APC mutations were detected in 33 patients and the highest frequency of these mutations identified in a region between codons 1306 and 1556. Some of the mutations were R1450 (a nonsense mutation at c.4348C>T, S1465FS3 (a frameshift mutation due to deletion of c.4393_4394delAG), R876 (c.2626C>T, nonsense), E1322 (c.3964G>T, nonsense), and E1379 (c.4135G>T, nonsense) [55] (Table 1). Moreover, they demonstrated that the frequency of mutations of the APC gene was found in 29.5% of 112 formalin-fixed paraffin-embedded tissues of sporadic CRC patients, which was inconsistent with other reports that the frequency of APC mutations is approximately 80% in sporadic non-hypermutated CRCs. These inconsistent results could be due to the small sample size (n=112) [55]. In contrast, Lee et al. demonstrated that APC mutations had the highest frequency among other genes with 72.3%, using targeted next-generation sequencing of 40 CRC candidate genes in 516 CRC patients [56]. Muzzny et al. also investigated 32 candidate genes in the 276 non-hypermutated and hypermutated CRC samples. They demonstrated that the rate of APC mutation frequency was about 81% of non-hypermutated CRCs [57]. Furthermore, Damak et al. also conducted a study in order to investigate the APC mutations in 124 sporadic CRC tumors and 41 lymph nodes. They identified five reported mutations: c.4160C>T, c.4385_4386delAGAG, c.4135insC, c.4348C>T, c.3990C>G, and 6 novel mutations in APC in the MCR: c.4254insA, c.4107insA, c.4263insG, c.3924insT, c.3923insG and c.4503insA [58] (Table 1).

Fig. 2. Schematic representation of APC gene mutations in different CRC subtypes. APC mutations are enriched in an area (exon 15) of the APC gene called mutation cluster region (MCR) which is spanning between codons 1285 and 1580.

T, S1465FS3 (a frameshift mutation due to deletion of c.4393_4394delAG), R876 (c.2626C>T, nonsense), E1322 (c.3964G>T, nonsense), and E1379 (c.4135G>T, nonsense) [55] (Table 1). Moreover, they demonstrated that the frequency of mutations of the APC gene was found in 29.5% of 112 formalin-fixed paraffin-embedded tissues of sporadic CRC patients, which was inconsistent with other reports that the frequency of APC mutations is approximately 80% in sporadic non-hypermutated CRCs. These inconsistent results could be due to the small sample size (n=112) [55]. In contrast, Lee et al. demonstrated that APC mutations had the highest frequency among other genes with 72.3%, using targeted next-generation sequencing of 40 CRC candidate genes in 516 CRC patients [56]. Muzzny et al. also investigated 32 candidate genes in the 276 non-hypermutated and hypermutated CRC samples. They demonstrated that the rate of APC mutation frequency was about 81% of non-hypermutated CRCs [57]. Furthermore, Damak et al. also conducted a study in order to investigate the APC mutations in 124 sporadic CRC tumors and 41 lymph nodes. They identified five reported mutations: c.4160C>T, c.4385_4386delAGAG, c.4135insC, c.4348C>T, c.3990C>G, and 6 novel mutations in APC in the MCR: c.4254insA, c.4107insA, c.4263insG, c.3924insT, c.3923insG and c.4503insA [58] (Table 1). Moreover, Huang et al. demonstrated that somatic APC mutations (especially frameshift mutations) are secondary events after germline mutations in some HNPCC patients. They identified 4 non-sense point mutations (all were C to T transition in CpG islands at codons 332,1338,1450) and 9 frameshift mutations (all were 1 bp insertion and or 1 bp deletion at codons 847,941,1454,1554,1935 and 907,1464,790,1416, respectively) [13]. Similarly, evaluation of 14 HNPCC adenomas with microsatellite instability revealed that the half of the colorectal adenomas represented somatic APC mutations. Five mutations were frameshift mutations including three 5-bp deletions of AAAAG at codons 1307–1311, one AG deletion at codons 1462–1465, and one 1-bp insertion at codons 1370–1371. The other two were nonsense mutations including R1450X and E1550X, suggesting the remarkable role of APC mutations in HNPCC [14].

2.2. Germline APC mutations

About 90% of patients with classical familial adenomatous polyposis (CFAP) have APC germline mutations (Fig. 1) [59]. Similar to sporadic CRCs, in most FAP tumors, one mutation in each allele are required for the development of CRC [17]. The majority of these
Moreover, Liu et al. identified that germline mutations within exons 5–8, 9–14 correspond to codons between 178 and 309 and codons between 409 and 1580, are associated with CFAP [60]. Moreover, Lipton et al. demonstrated that the central region of the APC gene between codons 1290–1400 are related to the most severe polyposis phenotype in FAP patients [61]. Further studies showed that 1061 and 1309 codons are two mutational hotspots which account for about 11% and 17% of all germline mutations, respectively [17].

Moreover, Liu et al. identified five APC mutations in Chinese FAP families that one of them, c.1548G > T (p.Lys516 Asn), a missense variant in exon 11, results in the destruction of APC protein. Furthermore, Zhang et al. identified a novel germline APC mutation in a Chinese FAP family which is associated with FAP. c.3418delC; (p. Pro1140-Leufs*25) is a heterozygous single nucleotide deletion in the APC gene which was detected by targeted next-generation sequencing and confirmatory Sanger sequencing. Likewise, this mutation took place in all of the family members with FAP and not in healthy family members and normal controls [63]. These results clearly support the clinical significance of APC mutations in the pathogenesis of CRC, suggesting the diagnostic and prognostic potency of these mutations in CRC initiation and progression. Table 1 summarizes somatic and germline mutations in APC.

**2.3. APC polymorphisms and CRC**

Various single nucleotide polymorphisms (SNPs) in the APC gene have been observed in CRC patients. In a case-control study performed in the Chinese Han population, genotyping ten single nucleotide polymorphisms (SNPs) were assessed and only rs11954856 polymorphism in the APC gene is related to sporadic CRC patients and normal controls that indicates this SNP has a role in predisposing to CRC cancer [64]. Moreover, it has been shown that rs11954856 polymorphism in the APC gene is related to sporadic CRC and could promote the expression levels of β-catenin. TCF7L1, TCF7L2 and LEF1 genes in the CRC patients [65]. Consistently, Li et al. found a novel SNP in the exon 15 of the APC gene which was associated with FAP.

<table>
<thead>
<tr>
<th>Somatic/Germline Mutations</th>
<th>Authors</th>
<th>Year</th>
<th>Mutations/variants</th>
<th>Type of Mutation</th>
<th>Type of CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatic</td>
<td>Gocke et al.</td>
<td>2000</td>
<td>5-base deletion at nucleotides 3961-3965</td>
<td>Frameshift</td>
<td>Sporadic</td>
</tr>
<tr>
<td></td>
<td>Prall et al.</td>
<td>2007</td>
<td>c.3881delA, c.3890T&gt;G, c.3915delA, c.3953delA, c.4012C&gt;T, c.4150delT, c.4480delG</td>
<td>Frameshift</td>
<td>Sporadic</td>
</tr>
<tr>
<td></td>
<td>Huang et al.</td>
<td>2012</td>
<td>c.19 + 647A &gt; G (rs2019720)</td>
<td>Synonymous substitution</td>
<td>Sporadic</td>
</tr>
<tr>
<td></td>
<td>Damak et al.</td>
<td>2015</td>
<td>c.4160C&gt;T, c.4385-4388delAGAG, c.4135insC, c.4348C&gt;T, c.3980C&gt;G, c.4254insA, c.4107insA, c.4263insG, c.3924insT, c.3923insG, c.4503insA</td>
<td>Frameshift</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Germline</td>
<td>Jauhri et al.</td>
<td>2017</td>
<td>c.4348C&gt;T, c.4393-4394delAGAG, c.2626C&gt;T, c.3964G&gt;T, c.4348C&gt;G, c.4135G&gt;T</td>
<td>Nonsense</td>
<td>Sporadic</td>
</tr>
<tr>
<td></td>
<td>Li et al. Boardman et al.</td>
<td>2001</td>
<td>c.357A&gt;G, IVS2-53→c, IVS4-17insT, IVS5-32→c, IVS5-33g→a</td>
<td>Silent</td>
<td>Hereditary (non-FAP, non-HNPCC families)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Frameshift</td>
<td>Hereditary (Ashkenazi Jews)</td>
</tr>
<tr>
<td></td>
<td>Liang et al. Zuber et al.</td>
<td>2012</td>
<td>c.3920T&gt;A (rs1801155, I1307K), c.3949G&gt;C (rs1801166, E1317Q), c.3924_3025insA</td>
<td>Missense</td>
<td>FAP</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Frameshift</td>
<td>Hereditary (FAP)</td>
</tr>
<tr>
<td></td>
<td>Li et al. Liu et al.</td>
<td>2015</td>
<td>c.4135G&gt;T, c.3131564T&gt;C (p.1125Val&gt;Ala), c.1548G&gt;C, c.1766T&gt;A, c.2510C&gt;G, c.3180_3184del, c.2016_2047del</td>
<td>Missense</td>
<td>Hereditary (FAP)</td>
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<td></td>
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<td></td>
<td>Frameshift</td>
<td>Severe FAP</td>
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<td>Severe FAP</td>
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<td>Sporadic</td>
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**Table 1**

Somatic and germline mutations of APC
Imperiale et al. suggested that a diagnostic panel consisting of 21 passive genetic marker panels for early diagnosis of CRC, which could be used as biomarkers in CRC [68,69]. For instance, Gocke et al. identified several mutations that are related to specific CRC stages in CRC: C4348T (codon: 1450) and C4216T (1406) in adenomas, G4189T (1397) and 4481delA (1494) in Duke’s A, C4348T (1450) and C4330T (1444) in Duke’s B, and 4662insA (1554) and 4468–4469delCA (1490) in Duke’s D stages [69]. Furthermore, they concluded that in APC WT tumors a distinct Wnt-signaling pathway was associated with different Duke’s stages. For instance, class 0 tumors (lacking APC mutation) conferred a worse prognosis than class 1 tumors (with a single detectable APC mutation). They demonstrated that class 0 tumors had no mutations in other WNT pathway genes. Therefore, they concluded that in APC WT tumors a distinct Wnt-independent signaling pathway could be a driving force behind CRC, suggesting an alternate molecular therapeutic intervention for APC WT tumors. Likewise, class 4 tumors had worst survival rate among all the subgroups examined. On the other hand, class 2 and class 3 were not associated with poorer survival [30]. Moreover, some specific APC mutants could be used as a prognostic biomarker to evaluate the sensitivity to tankyrase inhibitors (TNKS) in CRC cells. Tankyrase inhibitors (TNKss) are members of poly-ADP-ribose polymerases (PARPs) family that poly-ADP-riboseylate and down-regulate Axins, leading to overexpression of β-catenin. Therefore, tankyrase inhibitors have been developed to be a promising therapeutic agent in CRC treatment. Tanaka et al. demonstrated that drug-sensitive CRC cells possessed truncated forms of APCs lacking all seven β-catenin-binding 20AARs, which result in cell response to TNKss, whereas drug-resistance CRC cells possessed longer forms of APCs containing two or more 20AARs and did not respond to TNKss [71]. These results suggest that the identification of APC status could be a prognostic value procedure in the distinction of the two subgroups of CRC cells from TNKS-resistant or -sensitive ones.

Further studies showed that APC status could regulate the response to various chemotherapeutic agents. According to many roles of the APC in various dependent and independent Wnt/β-catenin pathways, any alteration in APC could result in resistance to cancer chemotherapeutic agents. The DNA alkylating agents such as methyl methane sulfonate (MMS) induce DNA damage that leads to cancer cell apoptosis. MMS has been used for many years as a chemotherapeutic drug in cancer treatment. However, it has been shown that BER mechanisms could repair the damaged DNA caused by alkylating agents, inhibit the efficiency of such drugs. APC acts as a DNA repair system inhibitor by interaction with DNA polymerase β (Pol-β) in single nucleotide base excision repair (SN-BER) and interaction with flap endonuclease 1 (Fen-1) in long-patch base excision repair (LP-BER) systems. Hence, APC intact function might increase the efficiency of alkylating drugs like MMS by the blockage of BER mechanisms. As a result, any alteration in APC has been associated with the increased ability of BER systems, results in chemotherapeutic resistant of cancer cells to MMS [72–75].

Histone deacetylases (HDACs) are involved in chromatin structure remodeling and gene expression by removing acetyl groups from hyper-acetylated histones in nucleosomes core particles. HDACs often suppress general gene transcription and aberrant activation of HDACs are in correlation with the development of many types of cancer including CRC. Recent findings suggest that several HDAC inhibitors such as valproic acid (VPA) and suberoylanilide hydroxamic acid (SAHA) might act as antitumor agents in many solid and hematologic cancers through activation of different apoptotic pathways. However, Huang et al. demonstrated that colon cancer cells expressing mutant APCs are relatively resistant to HDAC inhibitors. They proved that APC has a role in down-regulation of survivin, which is an anti-apoptotic protein. Therefore, cells containing mutant APCs are resistant to apoptotic drugs due to overexpression of survivin [76]. Consistent with this finding, Chen et al. reported that APC mutations regulate 5-fluorouracil (5-FU), an adjuvant chemotherapy-mediated treatment in CRC patients. The results indicated that 5-FU diminished the rate of all-cause death (hazard ratios = 0.257; P = 0.003) or CRC death (hazard ratios = 0.342; P = 0.028) only in CRC patients lacking APC mutations, while 5-FU has a reverse impact on CRC patients with APC mutations supporting the clinical significance of APC mutations in CRC treatment [77].

Moreover, the β-catenin inhibitory domain (CID) is known as...
another highly conserved regulatory domain in APC, which is located at the MCR, between the second and the third 20-aa repeats [78]. The CID in APC shows the cut-off value for pathological activation of the Wnt pathway and tumor transformation. Novel-lademan et al. demonstrated that CID-deleted truncated forms of APC increases β-catenin deubiquitination via reverse binding of β-TrCP and deubiquitinating enzymes (USP7) to the destruction complex, leading to over-activation of Wnt signaling and tumor transformation in CRC [79]. Taken together, these findings provide new data to better understand the role and the molecular mechanisms of APC mutations in the pathogenesis of CRC which could be utilized for personalized medicine in these patients.

4. Conclusion

CRC is one the most highly prevalent cancers globally, with a poor prognosis. Molecular pathways are well known for this disease and Wnt signaling is predicted to be the most common and important pathway involved in the pathogenesis of CRC [80]. In this review, we have discussed sporadic and various hereditary types of CRCs and the role of APC gene mutations in Wnt signaling-associated CRC development. We have discussed different types of CRCs (non-hypermutated and hypermutated CRC cells, sporadic and hereditary CRCs) and the role of the APC gene mutations in the Wnt signaling pathway associated with the development of CRC.

We have also briefly described the canonical Wnt/β-catenin signaling pathway and the role of other Wnt activating elements in CRC carcinogenesis. We have also considered the most recent advantages in diagnostic, prognostic and therapeutic values of APC mutations that confer a better comprehension in the application of genetic studies for management of different types of CRC.

It has been demonstrated that APC mutations might modulate diverse molecular targeted therapies in CRC patients. In line with this, Zhang et al. identified a small target-selective compound called truncated APC selective inhibitor-1 (TASIN-1). TASIN-1 exclusively induces apoptosis in APC mutant CRC cells, but not in APC WT CRC cells, by inhibition of cholesterol biosynthesis within cells. It has also been demonstrated that APC WT might be involved in the regulation of cholesterol homeostasis in a lipid-deficient environment caused by TASIN-1 [81]. This discovery could possibly lead to development and implication of more specific cholesterol biosynthesis inhibitors for prevention and intervention in APC mutant CRC patients. Further investigation should be performed to identify novel APC mutations and to exactly determine their association with disease characteristics in patients. These studies help to better understand as well as find more efficient therapeutic approaches that have great clinical significance in terms of the treatment of CRC associated complications.

Conflicts of interest

None.

References


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