APC

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Abstract

The *APC* gene is located at chr5q21 and is expressed in many tissues throughout the human body. In the colorectal epithelium in particular, *APC* functions as a critical suppressor of cancer initiation. Individuals who inherit inactivating mutations in one allele of the *APC* gene exhibit familial adenomatous polyposis (FAP) coli, an autosomal dominant syndrome characterized by the formation of a variety of benign lesions, particularly numerous adenomatous polyps of the colorectal epithelium.

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In the absence of preventative surgery to remove the source of these precancerous adenomas, FAP patients are highly susceptible to the development of colorectal cancer at an early age. Adenomas from FAP patients exhibit somatic mutations in the second allele of *APC*. Sporadically occurring colorectal adenomas in the general population frequently harbor biallelic *APC* mutations as well. The APC protein protects against adenoma formation in the colorectal epithelium at least in part by negatively regulating the canonical WNT signaling pathway. APC loss activates canonical WNT signaling, which coordinates changes in gene expression that promote proliferation over differentiation and cell survival over apoptosis. Ongoing research is focused on improving the accuracy of genetic screens for *APC* mutations, determining the extent to which colorectal cancers with *APC* mutations can be effectively treated with agents that downregulate canonical WNT signaling and testing the value of *APC* promoter hypermethylation as a diagnostic, prognostic, or predictive marker for other forms of cancer.

Keywords

APC • β-catenin • Canonical WNT signaling • Transcription • Colon • Colorectal • Cancer • CRC • Adenoma • Polyp • Polyposis • Familial • FAP • Tumor suppressor

APC is a 312-kilodalton protein expressed in numerous tissues throughout the human body. It is encoded by the *APC* gene located at chr5q21 (Senda et al. 2007). This locus was identified as the site of a tumor suppressor gene based on the observation of a deletion spanning this region in the germline of a patient affected by an autosomal dominant syndrome of colorectal cancer susceptibility known as familial adenomatous polyposis (FAP) coli (Heinen 2010) and inactivating mutations in a large open reading frame in other FAP patients (Senda et al. 2007). FAP is characterized by predisposition to various benign lesions, particularly numerous adenomas of the colorectal epithelium (Senda et al. 2007), some of which progress to colorectal cancer (CRC) at an early age in the absence of preventative surgery. The APC protein protects against tumor formation at least in part by negatively regulating the canonical WNT signaling pathway (Senda et al. 2007). APC interacts with glycogen synthase kinase 3β (GSK-3β) (Senda et al. 2007), Axin (Senda et al. 2007), and several other kinases and phosphatases (McCartney and Nathke 2008) to form a cytoplasmic complex with the transcriptional cofactor β-catenin (Senda et al. 2007). This complex (Fig. 1) promotes the sequential phosphorylation, ubiquitination, and proteolytic degradation of β-catenin (Senda et al. 2007). Activation of canonical WNT signaling is transduced through the disruption of this complex, accumulation of β-catenin in the cytoplasm, interaction with TCF family transcription factors, and translocation to the nucleus, with subsequent changes in gene expression (Senda et al. 2007). In the colorectal epithelium, the activation of canonical WNT signaling coordinates gene expression changes that promote proliferation over differentiation (McCartney and Nathke 2008) and cell survival over apoptosis (McCartney and Nathke 2008).

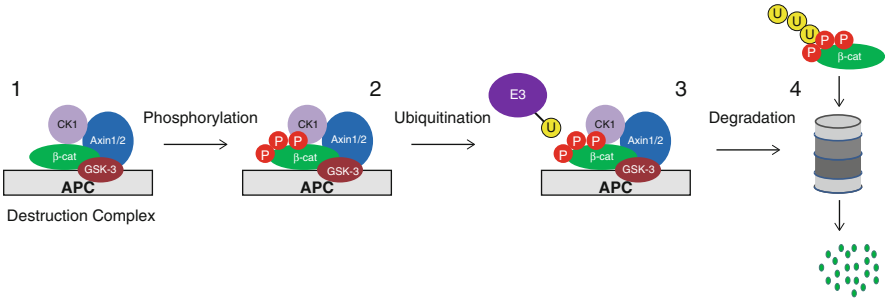

Fig. 1 APC is an essential component of the cytoplasmic destruction complex (1) which regulates negatively cellular β-catenin levels. This complex promotes the phosphorylation (2), ubiquitination (3), and proteasomal degradation (4) of β-catenin, a transcriptional cofactor required for canonical WNT signaling (Van der Auwera et al. 2008; Henrique et al. 2007; Hubers et al. 2012; Berrada et al. 2012; Half et al. 2009; Pack et al. 2013; Matuschek et al. 2010; Lynch and de la Chapelle 2003; Spigelman et al. 1989; Aretz et al. 2004; Lynch et al. 2007; Nielsen et al. 2007; Davila et al. 2006)

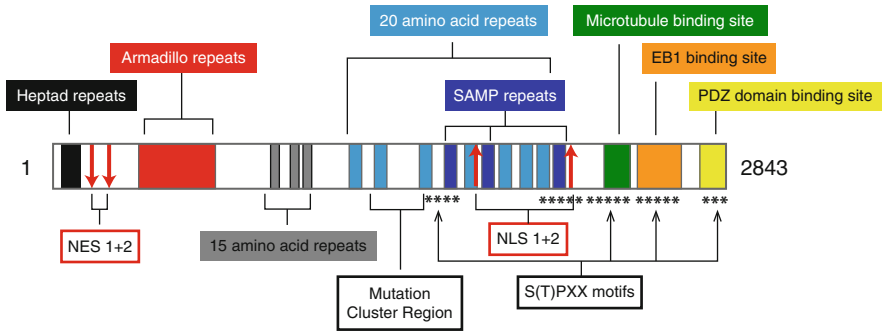

Fig. 2 The APC protein consists of 2843 amino acids whose major structural features include heptad repeats which mediate its dimerization (*black*) (Aziz et al. 2006), two nuclear export sequences (*down arrows*) [46], two nuclear localization sequences (*up arrows*) [45], clusters of S(T)PXX motifs (indicated by *asterisks*) which interact with A/T-rich DNA [50], armadillo repeats (*red*), and binding sites for microtubules (*green*) (Voronkov and Krauss 2013; Morton et al. 2011), the microtubule-associated protein EB1 (*orange*) (Anastas and Moon 2013), and PDZ domain-containing proteins (*yellow*). Interaction with Axins 1 and 2 is mediated by SAMP repeats (*dark blue*) (Henrique et al. 2007), while interaction with β-catenin is mediated by 15-amino acid repeats (*gray*) and 20-amino acid repeats (*light blue*) (Tonelli et al. 2000; Giardiello et al. 1993). Truncating mutations are observed most frequently in a central mutation cluster region, abolishing the Axin1/2 binding sites as well as the inducible interaction with β-catenin [68]

APC is an intrinsically unstructured scaffolding protein (Fig. 2) whose central region interacts with β-catenin constitutively through three repeats of 15 amino acids (Senda et al. 2007) and inducibly upon phosphorylation of seven additional repeats of 20 amino acids (McCartney and Nathke 2008) by GSK-3β (McCartney and Nathke 2008) and casein kinase I (CKI) (McCartney and Nathke 2008). This inducible interaction is required for APC to regulate negatively β-catenin levels

(Senda et al. 2007). The interaction of APC with Axin is mediated by three serine-alanine-methionine-proline (SAMP) repeats also located near the center of the protein (Senda et al. 2007). Additional domains in both its N- and C-terminal regions enable APC to interact with microtubules (Senda et al. 2007) and microtubule-associated proteins (Senda et al. 2007). These interactions reflect diverse functions of APC in cytoskeletal reorganization (McCartney and Nathke 2008) and cell adhesion (Senda et al. 2007) and in the control of apoptosis, cell division, and genomic stability (McCartney and Nathke 2008). APC contains multiple nuclear localization (Senda et al. 2007) and nuclear export sequences (Senda et al. 2007) which enable it to mediate the export of β-catenin to the cytoplasm (Senda et al. 2007) and to interact with chromatin (Senda et al. 2007). The C-terminus of APC contains clusters of S (T) PXX motifs that mediate binding to A/T-rich regions of DNA (Senda et al. 2007) and negative regulation of DNA replication (Lui et al. 2012). APC protein has been recently implicated in regulating the cellular response to replication stress (Lui et al. 2012) and base excision repair (McCartney and Nathke 2008). Finally, APC facilitates apoptosis (McCartney and Nathke 2008), both through transcriptional (McCartney and Nathke 2008) and transcription-independent mechanisms (Senda et al. 2007). The transcription-independent pro-apoptotic function is performed by an N-terminal fragment of APC following cleavage by caspase 8 (Lui et al. 2012). Thus, APC performs diverse functions at several different subcellular locations in order to suppress the development of CRC and other cancers.

Biology of the Target

Germline mutations in a single allele of *APC* are inherited by patients with familial adenomatous polyposis (FAP) coli and result in the production of a truncated APC protein (Senda et al. 2007) lacking most, if not all, normal functions. The extent of the inherited APC truncation influences the frequency of colorectal adenomas and extracolonic tumors in these patients, as well as the age of CRC onset (Heinen 2010). Truncated APC proteins also carry out acquired dominant functions that promote colorectal tumorigenesis (Lui et al. 2012) but that are likely of secondary importance to the loss of normal APC function. Adenomas arising in the colorectal epithelia of FAP patients exhibit inactivating somatic mutations in the second allele of *APC* (Heinen 2010).

The acquisition of biallelic *APC* mutations is an initiating event in the development of sporadic and familial colorectal tumors (Heinen 2010). *APC* mutations are observed in 50–80% of CRCs, many of which exhibit inactivation of both alleles (McCartney and Nathke 2008; Giles et al. 2003). More than 60% of *APC* mutations in CRC are found within a mutation cluster region located in Exon 15, resulting in the expression of truncated APC proteins of 1286–1513 amino acids or approximately the N-terminal half of the full-length protein (McCartney and Nathke 2008). Truncated proteins generally lack some or all of the 20-amino acid repeats required to regulate β-catenin levels, as well as the SAMP domains required to interact with

Axin. The consequences of APC loss are best understood in the context of CRC, where *APC* mutations drive tumor development by causing the accumulation of nuclear β-catenin and constitutive activation of canonical WNT signaling (McCartney and Nathke 2008), which in turn promote proliferation over differentiation (McCartney and Nathke 2008) and evasion of apoptosis (McCartney and Nathke 2008). The simultaneous loss of transcription-independent functions of APC additionally causes defects in mechanisms of apoptosis, cytoskeletal function, and control of cell division (McCartney and Nathke 2008).

Inactivating *APC* mutations occur less frequently outside of CRC but have been observed in tumors of the stomach (Giles et al. 2003), mouth (Uesugi et al. 2005), liver (Giles et al. 2003), pancreas (particularly solid-pseudopapillary tumors) (Giles et al. 2003), prostate (Giles et al. 2003), and breast (18%) (Virmani et al. 2001). Loss of APC function also occurs through epigenetic silencing, primarily due to promoter hypermethylation. Hypermethylation of the *APC* promoter region has been observed in carcinomas of the mouth (30%) (Uesugi et al. 2005), esophagus (15%) (Esteller et al. 2000), stomach (Esteller et al. 2000), liver (33%) (Esteller et al. 2000), pancreas (33%) (Esteller et al. 2000), bladder (10%) (Esteller et al. 2000), breast (45%) (Virmani et al. 2001; Van der Auwera et al. 2008), prostate (Henrique et al. 2007), lung (30–46%) (Virmani et al. 2001), colon and rectum (18%) (Esteller et al. 2000), and kidney (8%) (Esteller et al. 2000). In some cases, including bladder, prostate, lung, and breast cancers, the detection of *APC* mutations or epigenetic silencing is of diagnostic (Hubers et al. 2012; Berrada et al. 2012) and/or prognostic significance (Van der Auwera et al. 2008; Henrique et al. 2007). A variety of cancers exhibit constitutively activated canonical WNT signaling through mechanisms other than APC loss, including activating mutations in the *CTNNB1* gene encoding β-catenin (Giles et al. 2003).

Target Assessment

Genetic testing to assess *APC* germline status is indicated following either a clinical diagnosis of FAP based on a phenotype of polyp number or age of onset or the identification of an inherited *APC* mutation in a family member. *APC* mutation can be detected in peripheral blood lymphocytes by direct end-to-end sequencing of the *APC* gene, or less commonly by the protein truncation test (PTT), which detects a truncated APC protein synthesized in vitro from *APC* mRNA (Half et al. 2009). A genotype-phenotype correlation has been observed linking *APC* mutations in certain regions with an attenuated FAP (AFAP) variant in which affected individuals typically exhibit fewer than 100 colorectal polyps and later onset of disease (Heinen 2010). Identifying the germline *APC* mutation is useful for distinguishing AFAP and FAP (Half et al. 2009); however, these two phenotypes are more often clinically distinguished by polyp number. AFAP also differs from typical FAP in its lower associated risk of rectal polyps and rectal cancer (Half et al. 2009). Surgical recommendations for FAP and AFAP, respectively, are total proctocolectomy with ileal pouch-anal anastomosis (IPAA) and the less-radical colectomy with ileorectal

anastomosis (IRA) (Half et al. 2009). In addition to surgical resection and continued endoscopic screening, medications for FAP individuals to reduce polyp formation in the remaining large bowel epithelium include NSAIDs such as sulindac, aspirin, and celecoxib (Half et al. 2009).

Genetic testing to assess *APC* status is a critical step in FAP diagnosis, but the diagnostic and prognostic application of *APC* status in the context of various sporadic cancers remains in the developmental stages. The status of the *APC* gene in sporadic CRC is not generally tested because *APC* mutations do not seem to be strong indicators of prognosis in this context. In other tumor types where loss of APC function occurs more commonly through epigenetic rather than genetic mechanisms, disease-specific *APC* promoter hypermethylation in tumor tissue, urine (bladder cancer) (Berrada et al. 2012), sputum (lung cancer) (Hubers et al. 2012), and serum (colorectal cancer and breast cancer) (Pack et al. 2013; Matuschek et al. 2010), has been studied as a potential diagnostic marker (Hubers et al. 2012; Berrada et al. 2012) or marker of tumor progression, prognosis, or subtype (Van der Auwera et al. 2008; Henrique et al. 2007; Matuschek et al. 2010). Many of these studies have examined the methylation status of the *APC* promoter in the context of a larger panel of hypermethylated promoters. Several studies have shown some promise for prognosis in cancers of the breast, prostate, lung, liver, and bladder but have yet to be fully characterized as tools to advance clinical practice.

Role of the Target in Cancer

Rank: 10 (colorectal).

High-Level Overview

Diagnostic, Prognostic, and Predictive

Mutation of the *APC* gene causes familial adenomatous polyposis (FAP) coli which is characterized by more than 100 colorectal adenomas and often accompanied by extracolonic manifestations. Those affected carry a 100% lifetime risk of developing colorectal cancer by the age of 50 without prophylactic colectomy (Lynch and de la Chapelle 2003). Colorectal cancer attributable to FAP accounts for 1% of all CRC cases. In 60% of those with FAP, adenomas also develop in the duodenum (Spigelman et al. 1989). Due to the early onset of colorectal cancer in this patient population compared to the general population, the diagnosis of FAP leads to screening guidelines with consistent screening by colonoscopy and invariable planning for eventual surgical removal of the colon.

Current genetic testing guidelines call for evaluation of first-degree relatives of those with confirmed *APC* mutations or a clinical diagnosis of FAP. In 15–20% of adolescent FAP patients, a *de novo* mutation is discovered (Aretz et al. 2004). Commercial genetic testing for *APC* gene mutation has a sensitivity of 80%

(Lynch et al. 2007). For patients that show clinical signs of disease without an identifiable *APC* mutation, genetic testing for a biallelic mutation of *MUTYH* is indicated (Nielsen et al. 2007). This mutation leads to a phenotype that is similar to an attenuated FAP mutation.

Endoscopic screening of patients with FAP significantly reduces mortality attributable to colorectal cancer. Based on the available data on screening endoscopy, the American Society of Gastrointestinal Endoscopy recommends annual flexible sigmoidoscopy or colonoscopy for patients with a diagnosis of FAP starting between the ages of 10 and 12. For patients with an attenuated phenotype, endoscopic screening should start in their late teens to early twenties (Davila et al. 2006).

APC promoter hypermethylation indicates a poor prognosis in cancers such as prostate (Henrique et al. 2007) and breast (Matuschek et al. 2010) and defines a disease subtype in breast (Van der Auwera et al. 2008) and colorectal cancer (Fu et al. 2009). Further study of these correlations may lead to the emergence of *APC* promoter methylation as a predictive marker in certain contexts. In the context of CRC, loss of APC is associated with increased resistance to microtubule-stabilizing drugs such as Taxol or paclitaxel and increased sensitivity to the microtubule-destabilizing agent vinorelbine (Klotz et al. 2012). *APC* status in CRC has also been suggested to predict the effectiveness of COX-2 inhibitors, as COX-2 expression is activated by canonical WNT signaling (Giles et al. 2003).

Therapeutics

Due to the near certain development of colorectal cancer in the FAP patient population, prophylactic colectomy is recommended by the age of 20 (Davila et al. 2006). The pathologic staging of disease after surgery determines the need for adjuvant chemotherapy (Edge and Compton 2010). The determination of the proper surgical procedure between total proctocolectomy with ileal pouch-anal anastomosis (IPAA) and total abdominal colectomy with ileorectal anastomosis (IRA) requires an in-depth assessment of the patient polyp burden and location. IRA is preferred for patients with (1) low rectal polyp burden (<20 polyps), (2) small rectal lesions (<3 cm in diameter), and/or (3) an attenuated FAP phenotype (da Luz Moreira et al. 2009). The remaining rectal tissue imparts a greater lifetime risk of rectal cancer (Vasen et al. 2001). IPAA reduces the risk of rectal cancer by the near-complete removal of the rectal mucosa and is preferred to IRA. However, IPAA is more technically demanding than IRA, and the need for pelvic dissection has been associated with higher morbidity (Aziz et al. 2006). For female patients, recent studies have demonstrated reduced fertility and sexual function in women after IPAA compared to IRA (Olsen et al. 2003). Due to the risk of recurrent colorectal cancer in the rectal stump, ileal pouch, and anorectal cuff, scheduled lower endoscopy is recommended after surgery regardless of the procedure performed (Church and Simmang 2003).

The role of pharmaceutical agents in primary chemoprevention is unclear, although many drugs have shown efficacy as adjunct therapy for FAP patients

after surgery (Tonelli et al. 2000). Sulindac, a nonsteroidal anti-inflammatory drug, effectively reduces the size and number of rectal polyps (Giardiello et al. 1993). Celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, also has shown benefit as adjunct therapy for lower gastrointestinal polyp, although the use of COX-2 inhibitors is controversial due to reported increases in cardiac events (Steinbach et al. 2000). In a recent randomized controlled clinical trial, eicosapentaenoic acid, an omega-3 fatty acid metabolite, significantly reduced polyp number by 22% and polyp size by 29% (West et al. 2010).

Targeted therapeutic strategies for APC-deficient cancers have developed in response to the observation that APC-deficient CRC cells undergo cell cycle arrest and differentiation or apoptosis upon repression of canonical WNT signaling or restoration of APC function (Senda et al. 2007). Inhibitors of canonical WNT signaling have long been studied as potential therapeutic agents for APC-deficient CRC, particularly targeting components of the pathway that lie downstream of APC. Recent studies have identified small molecules that disrupt TCF/β-catenin transcription factor complexes (Voronkov and Krauss 2013) or block the effects of transcriptional target genes activated by canonical WNT signaling, particularly the critical c-Myc transcription factor (Morton et al. 2011). Components of the canonical WNT signaling pathway acting upstream of APC have also been targeted with some success in preclinical studies of APC-deficient CRC (Voronkov and Krauss 2013; Anastas and Moon 2013). β-catenin degradation has been stimulated either through a small molecule that partially restores cytoplasmic destruction complex function despite the absence of APC (Chen et al. 2009) or by alternative therapeutic mechanisms independent of the canonical WNT signaling pathway (Voronkov and Krauss 2013). Other pathways such as Vitamin D signaling and inhibition of the tankyrase enzyme downregulate canonical WNT signaling in CRC through mechanisms not yet fully understood (Voronkov and Krauss 2013; Anastas and Moon 2013). Despite the efficacy of these emerging WNT inhibitors in preclinical studies, substantial toxicity in humans is anticipated in some cases, due to the importance of the canonical WNT signaling pathway for stem-cell maintenance.

Novel therapeutic strategies have emerged recently to restore APC function in cancers with *APC* mutations through gene therapy (Macnab et al. 2011) or premature termination codon read-through (Zilberberg et al. 2010). In cancers with epigenetic silencing of *APC* such as breast and lung carcinomas, treatment with DNA demethylating agents such as decitabine inhibits canonical WNT signaling effectively *in vitro* (Virmani et al. 2001). MicroRNAs 135a and 135b, which downregulate APC at the mRNA level in a subset of CRCs, have shown early promise as therapeutic targets as well (Holleman et al. 2011). Finally, small interfering RNAs targeting mutant but not wild-type *APC* mRNA have the potential to silence the expression of truncated APC proteins and reduce proliferation *in vitro* (Chandra et al. 2012). Targeted therapeutics restoring APC function may act synergistically with established chemotherapeutic or chemopreventive agents such as NSAIDs to reverse CRC phenotypes *in vitro* and *in vivo* (Giles et al. 2003).

Preclinical Summary

APC loss occurs in the majority of CRCs, predominantly through genetic mutation (Esteller et al. 2000; Fu et al. 2009) but is not strongly predictive of prognosis. APC loss is also a common feature in other cancer types but occurs predominantly through promoter hypermethylation in these contexts (Esteller et al. 2000) and in some cases is associated with a poor-prognosis subset of disease (Van der Auwera et al. 2008; Henrique et al. 2007; Matuschek et al. 2010; Fu et al. 2009). *APC* promoter methylation status has shown promise in preclinical studies as a diagnostic or prognostic marker, often as part of a larger panel of gene promoters (Matuschek et al. 2010).

Targeted therapeutic strategies for APC-deficient cancers have focused either on targeting components of the canonical WNT signaling pathway downstream of APC (Voronkov and Krauss 2013; Morton et al. 2011) or on promoting β-catenin degradation through WNT-dependent (Chen et al. 2009) or WNT-independent mechanisms (Voronkov and Krauss 2013). Substantial toxicity is anticipated, yet some natural products found in the human diet may have the potential to promote β-catenin degradation through as yet-undefined mechanisms (Anastas and Moon 2013). Other strategies to restore APC function to cancer cells with *APC* mutations remain in the early stages of preclinical study (Macnab et al. 2011; Zilberberg et al. 2010).

Clinical Summary

The discovery of the role of *APC* gene mutation in the initiation of colorectal cancer has led to a greater understanding of the disease. Mutations of *APC* currently do not have a significant role in treatment algorithms for sporadic colon cancer, but its function in the canonical WNT signaling pathway portends a greater role in the future as more breakthroughs are achieved. For now, in the clinical realm, understanding the *APC* gene directly affects those patients afflicted with FAP. Those patients who receive genetic testing benefit by consistent screening and timely prophylactic surgery and by the diagnosis of at-risk family members. Current clinical research is aimed toward improving the accuracy of genetic screens and providing less-invasive screening methods. Although surgery remains the primary treatment modality, many clinical studies search for effective drugs to use in primary chemoprevention. Understanding the molecular mechanisms subsequent to *APC* mutation that underpin its effect on cancer initiation is an important way to generate new diagnostic options and therapeutic interventions for those patients with familial and sporadic colorectal cancer.

Anticipated High-Impact Results

- Determining the extent to which CRCs with mutations in *APC* can be safely and effectively treated by inhibitors of canonical WNT signaling, WNT-independent downregulation of β-catenin, *APC* gene therapy, or reagents promoting read-through of premature stop codons in the *APC* transcript

- Determining the extent to which CRCs and other cancers with *APC* promoter hypermethylation can be safely and effectively treated by demethylating agents, WNT-independent downregulation of β-catenin, or inhibitors of canonical WNT signaling
- Determining the value of *APC* promoter hypermethylation detectable in the serum as a diagnostic, prognostic, and/or predictive marker for therapeutic decision-making in the contexts of CRC and breast cancer
- Determining the value of *APC* promoter hypermethylation detectable in sputum as a diagnostic, prognostic, and/or predictive marker for therapeutic decision-making in lung cancer
- Determining whether *APC* promoter hypermethylation detectable in urine will be valuable as a diagnostic, prognostic, and/or predictive marker for therapeutic decision-making in bladder cancer
- Determining the extent to which *APC* status predicts CRC response to emerging therapeutic interventions

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