

# Computational and Literature Review Analysis of APC and E-Cadherin Regulation of Wnt/ $\beta$ -Catenin Signaling in Colorectal Cancer

By Hadassah Ho

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## ABSTRACT

Colorectal cancer (CRC) is characterized by a high mutational burden and complex genetic interactions that contribute to tumorigenesis, therapeutic resistance, and immune evasion. This study combines literature analysis with bioinformatic database query (via cBioPortal and Metascapes) to investigate how the overproduction of  $\beta$ -catenin contributes to CRC progression and therapeutic resistance, with the goal of identifying novel combinatorial treatment strategies. In the Wnt  $\beta$ -catenin signaling pathway, both APC mutations and the loss of E-cadherin drive aberrant production of  $\beta$ -catenin, promoting uncontrolled cell proliferation and chemoresistance. Normally, the  $\beta$ -catenin directly binds to the intracellular domain of E-cadherin, forming a complex essential for cell-cell adhesion and epithelial tissue integrity. In CRC, the  $\beta$ -catenin-E-cadherin link shifts from maintaining cell-cell adhesion to driving tumor progression, as the buildup of  $\beta$ -catenin in the cytoplasm results in less  $\beta$ -catenin at E-cadherin junctions. Combined with the overall loss of E-cadherin and  $\beta$ -catenin accumulation in the cytoplasm, this dysregulated process allows nuclear translocation to activate pro-invasive genes, driving CRC development. Finally, this study investigates the effects and potential treatments targeting APC mutations and the  $\beta$ -catenin-E-cadherin link and its effect on the proliferation of CRC by proposing a potential therapeutic strategy. By detailing a synthetic biology approach to reintroduce functional APC protein in colorectal cancer (CRC) models to restore regulation of  $\beta$ -catenin and reinforce E-cadherin-mediated cell adhesion. By reactivating normal Wnt signaling dynamics, this strategy aims to suppress uncontrolled proliferation and strengthen epithelial integrity compromised by APC loss.

**Keywords:** *Wnt/ $\beta$ -catenin signaling; APC truncation; E-cadherin interactions; colorectal cancer (CRC); synthetic protein therapy; cell adhesion; protein restoration therapy; Tumor microenvironment; Gene expression*

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## INTRODUCTION

Colorectal cancer (CRC) is the abnormal growth of cells in the colon or rectum. It is deemed to be among the major malignancies worldwide and occurs as a result of accumulation or a set of genetic and epigenetic modifications over time in different pathways that are proven to drive and transform the colonic epithelial cells into tumors (Alhadheq et al., 2023). According to the American Cancer Society, the incidence rate of CRC in people under the age of 55 has been increasing by 1% to 2% annually since the mid-1990s (*Colorectal Cancer Statistics | How Common Is Colorectal Cancer?*, n.d.). This trend is concerning, as CRC is the second leading cause of cancer-related deaths in the U.S., with cases projected to rise among younger adults. The issue isn't confined to the United States; similar patterns have been observed in Canada, New Zealand, Australia, and parts of Europe and Asia (*Colorectal Cancer Rising among Young Adults - NCI*, 2020). Studies from early 2023 revealed that 20% of CRC diagnoses in 2019 were in patients under 55, nearly double the rate from 1995. Additionally, rates of advanced disease in individuals under 50 have grown by about 3% per year. For 2023, it was estimated that 19,550 CRC diagnoses and 3,750 deaths would occur in people under 50. In most regions, the upward trend in younger adults began around 1995 (*Colorectal Cancer*, n.d.).

Cancer is caused by changes to genes, which can cause cells to grow and divide uncontrollably. Most genes that influence the growth and development of cancer are associated with oncogenes and tumor suppressor genes. Usually, these genes are not singular genes that function independently but rather networks of genetic and signaling pathways that work together to achieve a goal in the cell's day-to-day functions (Xiao et al., 2022). Due to this, it is important to target research in this area as soon as possible, emphasizing the urgency to develop preventive measures, early detection strategies, and effective treatments.

Genetic pathways refer to networks of interacting genes and their associated proteins that work together to carry out specific biological functions. Each step in a pathway typically involves a gene encoding a protein that influences the activity of downstream components, creating a cascade of events. Genes do not function in isolation within the cell but interact with each other, so genetic mutations may not only disrupt the functions of single genes but also impair the biological pathway activities within cellular signaling networks (Li et al., 2020). Instead of generally targeting tumor cells, which could affect neighboring healthy cells, through treatments such as chemotherapy, taking treatments to the source of cancer, the genetic influencers and pathways in the cell, would offer many opportunities to improve and specialize targets for cancer therapies (D et al., 2024; L. Zhang & Shay, 2017; Zhao et al., 2022).

The APC gene plays a critical role as a tumor suppressor within the Wnt signaling pathway, essential for regulating cell growth and division, as well as preventing uncontrolled proliferation that can lead to cancer. Mutations in APC can lead to the over production of  $\beta$ -catenin, disrupt key processes like cell division and

apoptosis, contributing to tumorigenesis (L. Zhang & Shay, 2017). With the disruption of the Wnt signaling pathway, there is a loss or downregulation of E-cadherin, a cell surface protein crucial for calcium-dependent cell-to-cell adhesion (van Roy & Berx, 2008). In healthy cells,  $\beta$ -catenin binds to E-cadherin at the cell membrane to form adherens junctions, which are crucial for cell-cell adhesion, cell polarity, and epithelial tissue integrity. In CRC, there is less  $\beta$ -catenin-E-cadherin binding, leading to upscaled presence of  $\beta$ -catenin in the cytoplasm. Finally, the buildup of  $\beta$ -catenin leads to the translocation to the nucleus, transcribing growth promoter genes. The combined weakness in the colon epithelial cells and the uncontrolled growth and division of cells create an ideal environment for CRC to progress.

Analysis of different interconnected and overlapping gene pathways that relate to colorectal cancer allow for the visualization of similarities and connections to further research in therapeutic and diagnostic processes. Using data from cBioPortal, a user-friendly platform for exploring cancer genomics data and their clinical significance, allows integration of large-scale datasets from sources like TCGA (The Cancer Genome Atlas). With a focus on mutations, copy number alterations, expression changes, and pathway disruptions, this literature review also incorporates analysis from Metascape and Cytoscape, web-based platforms for functional enrichment and pathway analysis which help researchers explore the biological significance of gene lists. Through a mix of existing research and real-life data analysis, this paper uncovers the intricate relationships between genes and pathways in colon cancer, especially in cell communication and junction, which can lead to a better understanding of the disease's mechanisms and identify potential targets for treatments or biomarkers for diagnosis.

## **METHODS**

Somatic mutation data for colorectal cancer were obtained from cBioPortal for Cancer Genomics using the Colon Adenocarcinoma (TCGA, GDC) dataset (study ID: coad\_tcga\_gdc), generated through The Cancer Genome Atlas. Within cBioPortal, the "Mutations" genetic profile was selected and all available profiled samples in the COAD dataset were included. Genes were ranked according to mutation frequency, and the total number of mutations, number of samples with at least one mutation, and overall mutation frequency (%) were recorded. The ten most frequently mutated genes were exported for further analysis, with particular attention given to APC and TP53 due to their established roles in colorectal tumorigenesis. To evaluate functional interactions among clinically mutated genes, the gene list derived from cBioPortal was uploaded into Metascape for pathway enrichment and network analysis. The analysis was performed under default "Express Analysis" settings with Homo sapiens selected as the species. Ontology sources included GO Biological Processes, KEGG Pathway, and Reactome Gene Sets, and protein-protein interaction enrichment was generated using default parameters with MCODE clustering to identify functional modules. The resulting enrichment tables and global interaction

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network maps were examined to identify clusters related to cell–cell adhesion, cell junction organization, cytoskeletal regulation, morphogenesis, and extracellular matrix organization.

Finally, supporting literature was identified through structured searches in PubMed and Google Scholar using combinations of keywords including “colorectal cancer,” “APC mutation,” “TP53,” “Wnt/ $\beta$ -catenin,” “E-cadherin,” and “tumor microenvironment.” Priority was given to peer-reviewed primary research articles and recent review papers (2015–2024) that included mechanistic, genomic, or TCGA-based analyses relevant to colorectal cancer. No additional statistical transformations were applied beyond the default outputs provided by cBioPortal and Metascape.

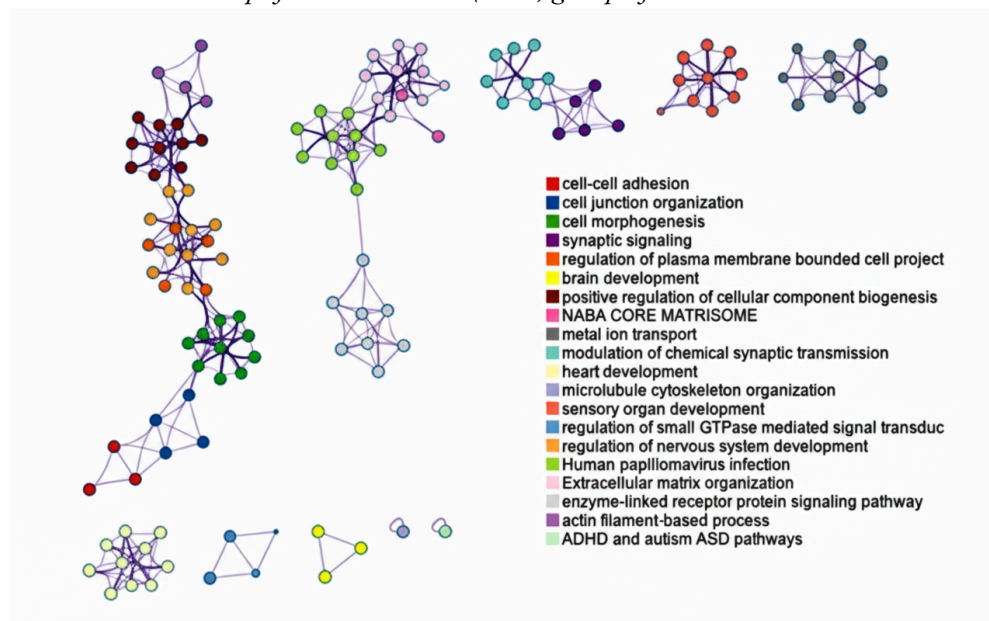
## RESULTS

### Bioinformatic database query

The APC gene is the highest mutated gene in this analysis, which agrees with the literature, with a mutation rate of 71.8% across 464 samples (Table 1), demonstrating a concerning connection between CRC and the disruption of the Wnt/ $\beta$ -catenin signaling pathway (*cBioPortal for Cancer Genomics*, n.d.)

**Figure 1**

*Global interaction map of colorectal cancer (CRC) gene profiles*



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*Note. This image demonstrates how CRC-associated genes cluster into distinct but interconnected functional modules. Notably, several of the connected clusters correspond to cell-cell adhesion, cell junction organization, and cytoskeletal regulation, etc. all of which are central to the Wnt/ $\beta$ -catenin and E-cadherin pathways. Additionally, this visualization highlights the extensive crosstalk between adhesion-related genes and broader signaling processes such as morphogenesis, extracellular matrix organization, and enzyme-linked receptor pathways which demonstrate how APC or  $\beta$ -catenin affects multiple cellular systems (Zhou et al., 2019). Created using Metascape web app [web tool] with clinical data from cBioPortal TCGA COAD study. From Metascape, n.d., <https://metascape.org>; cBioPortal for Cancer Genomics n.d., [https://www.cbioportal.org/study/summary?id=coad\\_tcg\\_a\\_gdc](https://www.cbioportal.org/study/summary?id=coad_tcg_a_gdc).*

**Table 1**

*First 10 most commonly mutated genes in CRC clinical data*

| Gene   | Total Number of Mutation | Number of samples with one or more mutations | Frequency |
|--------|--------------------------|----------------------------------------------|-----------|
| APC    | 490                      | 308                                          | 71.8%     |
| TP53   | 254                      | 237                                          | 55.2%     |
| TTN    | 616                      | 202                                          | 47.1%     |
| KRAS   | 186                      | 183                                          | 42.7%     |
| PIK3CA | 154                      | 127                                          | 29.6%     |
| SYNE1  | 255                      | 122                                          | 28.4%     |
| MUC16  | 277                      | 121                                          | 28.2%     |
| FAT4   | 182                      | 99                                           | 23.1%     |
| RNF43  | 163                      | 86                                           | 20%       |
| ZFHX4  | 121                      | 86                                           | 20.0%     |

*Note. Adapted from clinical data accessed from cBioPortal's Colon Adenocarcinoma (TCGA, GDC) dataset, shows that the APC gene is one of the most commonly mutated gene found in 429 profiled clinical samples in CRC patients with a 71.8% mutation frequency (cBioPortal for Cancer Genomics, 2026).*

## LITERATURE REVIEW

### **The Wnt/ $\beta$ -Catenin Pathway in CRC**

The Wnt/ $\beta$ -catenin pathway is activated when Wnt binds to its core receptor complex. Without Wnt, cytoplasmic  $\beta$ -catenin is phosphorylated and targeted for degradation by a protein complex containing GSK3 $\beta$ , CKI, Axin, and APC (Figure 2). The APC gene plays a crucial role in regulating this pathway (He & Gan, 2023; L. Zhang & Shay, 2017).

This pathway is responsible for many roles in cell regulation, such as proliferation, cell maintenance, and metastasis. Across different sources of literature, an observable pattern is observed regarding the Wnt pathway's impact on CRC, self-renewal of cancer stem cells and tumor microenvironment (TME) (Ménier et al., 2015; Nguyen et al., 2019; Zhao et al., 2022). Firstly, Wnt signaling plays a critical role in maintaining self-renewal, survival, and proliferation of cancer stem cells (CSCs), a subpopulation of tumor cells with stem cell-like properties. These CSCs are thought to drive tumor initiation, growth, recurrence, and metastasis due to their ability to regenerate tumors and resist conventional therapies such as chemotherapy and radiation (Zhao et al., 2022). Wnt signaling aids CSCs in surviving these treatments, enabling them to repopulate the tumor, leading to recurrence. Additionally, the pathway enhances CSC plasticity, allowing these cells to adapt to different microenvironments during metastasis, further emphasizing its role in tumor progression (Zhao et al., 2022).

### **APC as a Gatekeeper of Wnt Regulation and Cell Integrity**

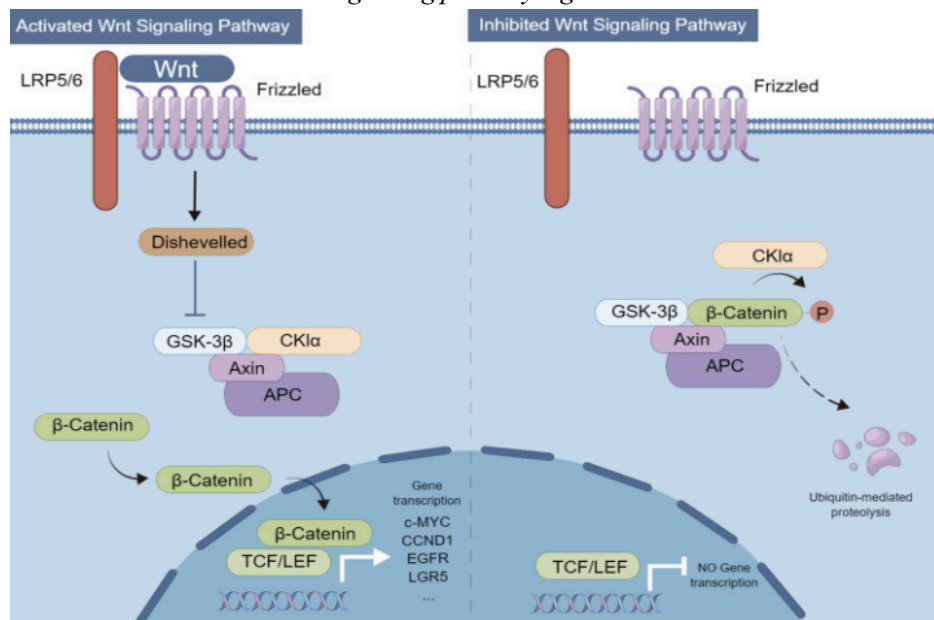
Loss of APC results is one of the main perpetrators of an increase of Wnt signaling activity, which leads to overexpression of oncogenic target genes in the presence of tumorigenesis. It regulates the binding of phosphorylated  $\beta$ -catenin to the ubiquitin-mediated proteolytic pathway in the cytoplasm. When Wnt is present, this process is halted, causing  $\beta$ -catenin to accumulate in the cytoplasm and translocate to the nucleus (Fig. 2), where it activates target gene expression (D et al., 2024).

By negatively regulating canonical Wnt signaling, APC plays a crucial role in counteracting cell proliferation, promoting differentiation, facilitating apoptosis, and ultimately suppressing tumor progression (Barua & Hlavacek, 2013). Beyond its cytoplasmic function, APC interacts with  $\beta$ -catenin in the nucleus, further reinforcing its antagonistic effect on Wnt signaling. This regulatory role is particularly significant in colorectal cancer (CRC), as inherited mutations in the APC gene lead to the formation of adenomatous polyps, which frequently progress to CRC before the age of 40 (Hankey et al., 2018). Notably, APC mutations

represent one of the earliest genetic events in CRC development, setting the stage for further oncogenic changes. In addition to its involvement in the Wnt pathway, APC contributes to cytoskeletal organization and cell migration, while also localizing to key cellular structures such as kinetochores, centrosomes, and microtubules (D et al., 2024). This means that a malfunction or mutation of the APC gene can result in much more than abnormal expression of genes. It affects the structure and organization of the cell, further contributing to the development of tumors (Barua & Hlavacek, 2013).

**Figure 2**

*Activated and Inhibited Wnt signaling pathway regulation*



*Note. Illustrating that when Wnt is present,  $\beta$ -catenin stabilizes and activates gene transcription, while in its absence,  $\beta$ -catenin is degraded, preventing gene activation. This diagram is reprinted from Zhao, H., Ming, T., Tang, S., Ren, S., Yang, H., Liu, M., Tao, Q., & Xu, H. (2022). Wnt signaling in colorectal cancer: Pathogenic role and therapeutic target. *Molecular Cancer*, 21(1), 144. <https://doi.org/10.1186/s12943-022-01616-7>*

### APC Truncation Mutations in correspondence with CRC tumorigenesis

A growing body of evidence suggests that APC truncation is one of the most prevalent mutations in CRC (Wang et al., 2025). In genetics, a truncated protein is one that is incomplete or prematurely shortened due to a mutation, often caused by a nonsense or frameshift mutation that introduces a premature stop codon (Hankey et al., 2018). APC truncation either misshapen or eliminates its  $\beta$ -catenin-binding domain completely,

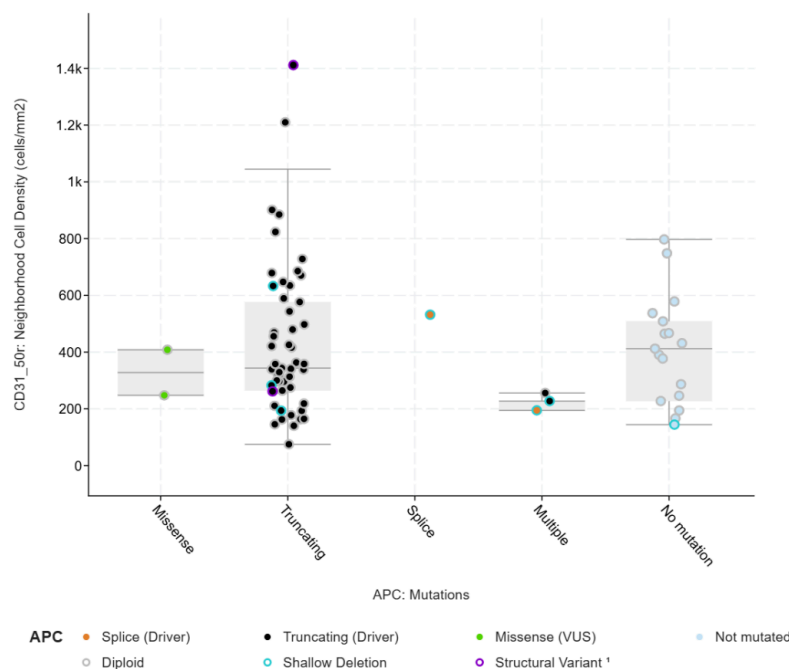
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preventing  $\beta$ -catenin binding and degradation which results in its pathological stabilization. As a result,  $\beta$ -catenin accumulates in the cytoplasm and nucleus, driving tumorigenesis through target gene activation (Barua & Hlavacek, 2013). Finally, a majority of all APC mutations are truncated, especially in terms of cellular density around the tumor or the TME (Figure 3).

In general, CRCs exhibit a strong preference for truncating mutations in a specific 200-amino-acid region of the APC protein, known as the mutation cluster region. This unusual pattern of nonsense and frameshift mutations differs from typical tumor suppressor genes and suggests that these specific alterations give tumors a growth advantage (Schatoff et al., 2017). To explain this phenomenon, the "just right" hypothesis proposes that precancerous cells require an optimal level of Wnt activation—neither too low nor excessively high—to stop driving malignant transformation. Since the degree of Wnt activation is influenced by the location of APC truncation, understanding this relationship is crucial for deciphering CRC progression. However, despite its significance, experimental evidence remains limited on why specific truncation sites are critical for tumor development (Schatoff et al., 2017).

**Figure 3**

*APC mutations' effect on presence of endothelial cells in the TME*



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*Note. This chart illustrates the relationship between APC mutations (classified into different types such as truncating, missense, splice, multiple, and no mutation) and CD31+ neighborhood cell density, measured in cells/mm<sup>2</sup>. CD31 is often used as a marker of vascular endothelial cells, so the density here reflects the presence of endothelial cells in the tumor microenvironment. Here, this figure illustrates the distribution and frequency of different types of APC mutations. Created by author (2026), using cBioPortal web app and data from cBioPortal TCGA COAD study, [https://www.cbioportal.org/study/summary?id=coad\\_tcg\\_a\\_gdc](https://www.cbioportal.org/study/summary?id=coad_tcg_a_gdc)*

### **E-Cadherin and Cellular Adhesion in Epithelial Cells**

Adherens junctions form when the extracellular domain of E-cadherin forms homophilic, calcium-dependent bonds with other E-cadherin molecules. By maintaining the epithelial barrier by anchoring cells together and providing stability, these bonds not only help support the function of the colon but also ensure proper regulation of cell-to-cell signaling especially involving proliferation, migration, and differentiation (Daulagala et al., 2019). Intracellularly, the cytoplasmic tail of E-cadherin associates with  $\beta$ -catenin, which in turn links the adhesion complex to  $\alpha$ -catenin and the actin cytoskeleton, forming a structurally integrated adhesion network. This E-cadherin/ $\beta$ -catenin complex is essential for maintaining epithelial barrier integrity by anchoring neighboring cells and preserving tissue architecture (Valenta et al., 2012). Because of this, the formation of tissue barrier linked with the actin cytoskeleton forms a mechanical network that prevents cells from moving apart which affects the spread and metastasis in cancer (Daulagala et al., 2019).

## **DISCUSSION**

### **Disruption of E-Cadherin/ $\beta$ -Catenin Interaction due to APC dysfunction**

Although aberrant Wnt signaling driven by APC mutation and E-cadherin-mediated cell-to-cell adhesion are often treated as distinct biological processes, both converge on regulation of the  $\beta$ -catenin complex, creating a functional connection between them (Christou et al., 2017). The E-cadherin/ $\beta$ -catenin complex is essential for maintaining epithelial integrity by preserving cell-cell adhesion and tissue polarity; disruption of this complex therefore has consequences that extend beyond adhesion alone, directly influencing  $\beta$ -catenin availability and downstream Wnt signaling. In healthy colon cells,  $\beta$ -catenin works to anchor E-cadherin to the actin cytoskeleton, which stabilizes adherens junctions and preserves epithelial organization (Valenta et al., 2012). Under normal physiological conditions,  $\beta$ -catenin exists in two distinct pools one of which is located in the cell's membrane and works to stabilize E-cadherin-mediated cell adhesion and the other located in the cytoplasm that is tightly regulated by the APC destruction complex. Together, APC gene and E-cadherin both work to regulate Wnt signaling. While the APC protein produced by the gene identifies and binds to  $\beta$ -catenin, marking it for degradation by the destruction complex, E-cadherin sequesters  $\beta$ -catenin at the membrane to

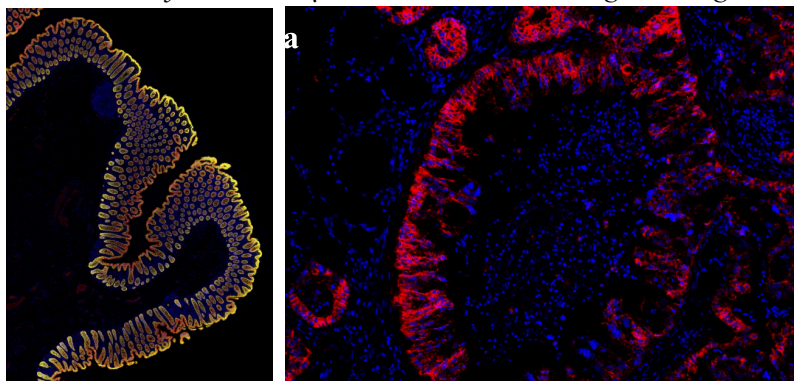
maintain junctional stability. Both processes keep the activation of the Wnt signaling pathway to a minimum, stopping uncontrolled cell proliferation and growth (X. Zhang et al., 2017).

However, in CRC, the activation of the Wnt signaling due to the dysfunction of the APC gene and the destruction complex, leads to the reduction of E-cadherin. This reduction is followed by the increase of free  $\beta$ -catenin to become available to activate Wnt target genes, driving the epithelial-mesenchymal transition (EMT) and contributing to cancer progression (Heuberger & Birchmeier, 2010). In addition to that, when the APC gene no longer functions as intended,  $\beta$ -catenin is no longer efficiently degraded and accumulates in the cytoplasm, shifting the equilibrium away from the membrane-bound pool. This redistribution weakens E-cadherin-mediated adhesion and promotes  $\beta$ -catenin's nuclear translocation, where it activates oncogenic Wnt target genes that drive uncontrolled proliferation and early tumorigenesis (Tian et al., 2011).

In the healthy tissue (Fig. 4a), strong yellow fluorescence indicates robust E-cadherin/ $\beta$ -catenin co-localization at the cell membrane, reflecting stable adherens junctions and intact epithelial polarity. Cytokeratin staining (red) outlines well-organized epithelial layers, and DAPI (blue) highlights evenly distributed nuclei, consistent with normal tissue architecture. In contrast, the colon cancer tissue (Fig. 4b) shows a marked loss of yellow signal, suggesting weakened or absent E-cadherin/ $\beta$ -catenin binding at cell junctions ("E-Cadherin and  $\beta$ -Catenin Interactions," n.d.). The disorganization of red cytoke-  
 ratin staining and accumulation of  $\beta$ -catenin in the cytoplasm further reflect epithelial breakdown and disrupted adhesion (Christou et al., 2017). These observations directly support the hypothesis that APC loss and aberrant Wnt signaling drive  $\beta$ -catenin dissociation from E-cadherin, allowing its nuclear translocation and activation of oncogenic transcriptional programs .

#### Figure 4

*Visualization of E-cadherin/ $\beta$ -catenin interaction through staining*



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*Note. a) E-cadherin/ $\beta$ -catenin interaction visualized in healthy colon tissue with NaveniFlex™ Tissue. Interaction in yellow, co-stain with cytokeratin in red, and cell nuclei in blue (DAPI) (“E-Cadherin and  $\beta$ -Catenin Interactions,” n.d.). b) E-cadherin/ $\beta$ -catenin interaction visualized in colon cancer, detection with NaveniFlex Tissue (“E-Cadherin and  $\beta$ -Catenin Interactions,” n.d.). Both of these images are reprinted from E-cadherin and  $\beta$ -catenin interactions. (n.d.). Navinci. Retrieved October 7, 2025, from <https://navinci.se/applications/assay-database/e-cadherin-and-beta-catenin-interactions/>*

### **Wnt/ $\beta$ -Catenin Pathway and the Tumor microenvironment**

Beyond its role in cell cycle regulation, signaling, and adhesion, the Wnt signaling pathway significantly contributes to cancer drug resistance, including chemotherapy and immunotherapy resistance in CRC (Zhao et al., 2022; Zhu & Li, 2023). Chemotherapy remains a primary treatment for CRC, but drug resistance limits its effectiveness. Studies suggest that aberrant Wnt signaling is a key driver of chemotherapy resistance, highlighting the need for targeted therapies that can inhibit this pathway.

Furthermore, increasing evidence suggests that cancer stem cells, non-coding RNAs, and the tumor microenvironment (TME) contribute to Wnt-mediated drug resistance. The Wnt/ $\beta$ -catenin pathway interacts with the TME, influencing cancer progression and modulating tissue morphogenesis during embryogenesis and repair (Zhao et al., 2022). One critical mechanism of Wnt-driven resistance is its role in suppressing T-cell infiltration within the tumor, which weakens immune responses in cancer patients. The activation of Wnt/ $\beta$ -catenin signaling in the TME has been reported to reduce T-cell infiltration, leading to immune evasion and resistance to immunotherapy (Yeoh et al., 2021).

There are significant efforts focusing on delineating tumor evolution and the underlying molecular mechanisms of drug resistance linked to these signaling pathways. Numerous studies have revealed that genetic mutations and/or epigenetic alterations of these pathways contribute to drug resistance (Yeoh et al., 2021). A big part of the issue lies in the TME, where tumors can essentially “mask” their presence to the human immune cells. In fact, the TME cells are a double-edged sword as they play both pro- and anti-tumor roles. The interaction of the tumor-infiltrating cells (TIC) with the cancer cells induces the polarization of the tumor initiating cells, exhibiting an antagonist phenotype (Ben Hamouda & Essafi-Benkhadir, 2023).

In this case, Wnt pathway signaling shapes the TME by regulating processes such as angiogenesis, inflammation, and immune responses, all of which contribute to tumor progression and resistance to therapies. It modulates inflammatory responses and immune cell infiltration within the tumor microenvironment, impacting tumor progression and response to therapy. Activation of Wnt/ $\beta$ -catenin signaling can lead to the

release of inflammatory cytokines, creating a pro-inflammatory environment that supports tumor development and progression (Méniel et al., 2015).

In addition to that, weakened adhesion and structure of colon cells due to the loss of actin cytoskeleton binding, creates a favorable environment for the migration and spread of malignant CRC (Zhang et al., 2023). Destabilization of adherens junctions reduces  $\beta$ -catenin sequestration at the membrane, increasing its cytoplasmic and nuclear availability and amplifying pro-proliferative and pro-migratory transcriptional responses. This structural breakdown promotes epithelial-to-mesenchymal transition (EMT), enabling cancer cells to detach, invade surrounding tissues, and acquire enhanced migratory ability (Christou et al., 2017). Concurrently, altered adhesion dynamics reshape the tumor microenvironment by modifying cell-matrix interactions, extracellular matrix remodeling, and mechanotransduction signaling. These changes influence stromal fibroblasts, immune cell infiltration, and inflammatory signaling, collectively creating a permissive niche that supports tumor invasion, immune evasion, and metastatic spread (Daulagala et al., 2019).

## **FUTURE RESEARCH**

As described previously, the mutation of the APC gene impacts both aspects in a negative way. Reinstating its function or introducing a non-truncated binding site for  $\beta$ -catenin that would eliminate the risk of its buildup in the cytoplasm. Due to this, this study proposes a synthetic biology-based strategy that would both eliminate cell-to-cell junction weaknesses and limit the transcription of growth target genes. With the goal of reinstating normal Wnt signaling by using synthetic APC protein expression, this approach involves a two-stage experimental model designed to test whether reintroducing functional APC can counteract  $\beta$ -catenin overaccumulation and abnormal Wnt activation. In the first stage, the human APC gene will be cloned and expressed in yeast cells (Rajeshkannan et al., 2022), taking advantage of their genetic tractability to produce and verify recombinant modified APC protein that only produces the section that binds with  $\beta$ -catenin (due to APC protein large size). The second stage will test the purified protein in SW480 human colorectal adenocarcinoma cells (Justin W. E. Lim, n.d.), a model characterized by APC loss and strong Wnt-driven proliferation. This proof-of-concept project seeks to establish a foundation for developing combinatorial therapies that use synthetic biology to reactivate disrupted tumor suppressor pathways in CRC. Importantly, reintroducing functional APC protein fragments may reduce cytoplasmic  $\beta$ -catenin accumulation, prevent its nuclear translocation and promote its stabilization at E-cadherin junctions. This could reinforce epithelial cell adhesion and polarity, which mitigates one of the key structural and signaling disruptions in CRC progression.

If this proposal succeeds and functions as intended, then the main signaling pathways in CRC are able to subsequently function and be able to slow or even prevent the development of cancer cells. Thus, these experiments could possibly set a baseline for combinatorial therapies that use synthetic biology to reactivate

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tumor suppressor pathways and strengthen epithelial integrity in colorectal cancer. Secondly, this type of treatment, if expanded upon, can have a better and more regionalized impact on cancer cells. Unlike chemotherapy and other more invasive treatments, this one can be personalized to fit each patient individually. Finally, like many up-and-coming therapeutic strategies, this method could be applied to a lot of different cancers based on its gene expression; by reinstating inactivated critical pathways, this treatment could even be more generalized to many diseases than just cancer.

**CONCLUSION**

This study combines literature review with data analysis to highlight the critical role of APC dysfunction and  $\beta$ -catenin overproduction in CRC development, progression, and resistance to therapy. The presence of APC mutations, especially truncations, in CRC are present in most patient cases, which promotes the nuclear accumulation and transcriptional activation of oncogenic targets within the Wnt signaling pathway. The disruption of the APC/ $\beta$ -catenin/E-cadherin axis not only leads to a breakdown in cell adhesion, uncontrolled cell proliferation, and immune evasion, but also plays a significant role in contributing to the therapeutic resistance in the TME. Elucidating the interplay among these components within the Wnt signaling pathway, particularly in relation to key target genes, offers a strategic framework for designing future combinatorial therapies. Future directions include testing synthetic APC protein as a therapeutic tool to rebalance  $\beta$ -catenin levels and stabilize its interaction with E-cadherin, thereby restoring cell adhesion and reducing Wnt-driven tumor progression. Such an approach could pave the way for innovative combinatorial treatments that repair disrupted signaling networks in CRC.

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