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Investigating the WNT and TGF-beta pathways alterations and tumor mutation burden in young-onset colorectal cancer

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Colorectal cancer (CRC) is the third most common cancer in the United States. Recent epidemiological evidence demonstrates an increasing incidence of young-onset CRC cases, defined as CRC cases in individuals 50 years old or younger. Studies have established that alterations in both the WNT and TGF-Beta signaling pathways have contributed to CRC development. While this is well understood, the comprehensive analysis of WNT and TGF-Beta pathway alterations in young-onset CRC cases has yet to be investigated. Here, we conducted a comprehensive bioinformatics analysis of mutations associated with each of the WNT and TGF-Beta signaling pathways according to age (≤ 50 years old versus > 50 years old) utilizing published genomic data from the cBioPortal. Chi-square results demonstrated no significant difference in WNT alterations between young-onset CRC and those > 50 years old. However, across all age groups, WNT alterations were frequently found in rectal cancers. We also found that WNT alterations were associated with better outcomes. The mutations associated with TGF-beta were observed at a higher rate in older CRC patients when compared to those ≤ 50 years old. Additionally, these mutations were found more frequently in colon primaries.

Colorectal cancer (CRC) is the third most common cancer in the United States and the second most common cause of cancer-related deaths worldwide[1]. Previously, the median age at diagnosis was 68 and 72 years old for men and women, respectively. However, more recent evidence demonstrates an increasing incidence of young-onset CRC cases in the United States and a number of other high-income countries[2]. Young-onset CRC has been defined as cases of CRC occurring in individuals 50 years-old or younger. This increasing incidence is thought to account for approximately 10% of all new cancer diagnoses. Furthermore, studies have demonstrated a concomitant rise in CRC mortality, especially within younger patient populations[3,4]. Young-onset CRCs have been characterized by more advanced stages at time of diagnosis and poorer cell differentiation[5]. Studies so far revealed that the young-onset CRC could have distinct molecular characteristics like CIMP-low and LINE-1 hypomethylation[6,7]. However, the molecular features of the young-onset CRC are not thoroughly delineated.

Several signaling pathways have been implicated in CRC carcinogenesis, with the WNT signaling pathway and the TGF-beta pathway being well recognized for their role in the process. WNT signaling acts as a primary driving force for adult stem cell self-renewal and cell fate specification in several tissues, including the intestine and colon[8]. This signaling is highly regulated by numerous tumor suppressor genes, with mutation or silencing of WNT tumor suppressors leading to sustained WNT-Beta Catenin signaling (Fig. 1a). Unchecked activity provides cells with self-renewing growth properties and is associated with therapy resistance. Major contributors leading to the development of colorectal cancer include the loss of expression in APC, AXIN1, AXIN2, GKS3B, and RNF43.

Similarly, the TGF-beta signaling pathway also plays a key role in cell proliferation, with alterations acting as pivotal events in CRC carcinogenesis[9]. In normal intestinal epithelium, TGF-beta serves as a tumor suppressor

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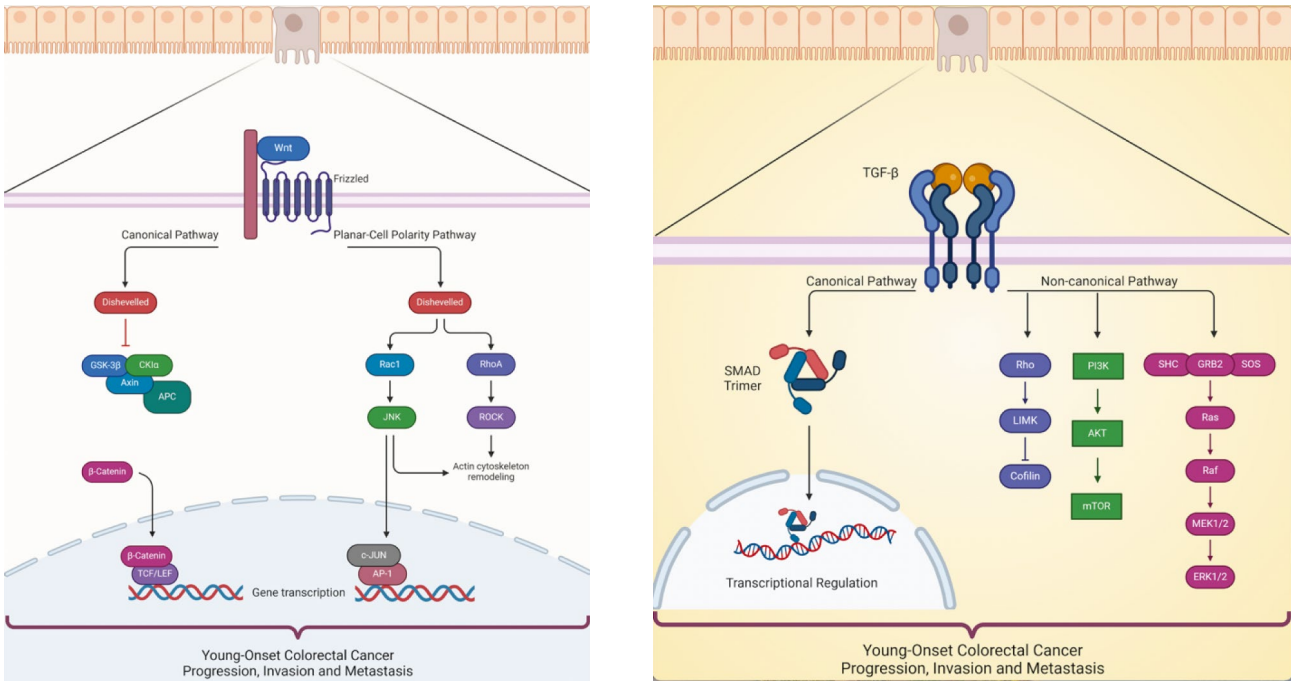

Figure 1. (**a**). Depicts the WNT signaling pathway (created by using biorender version 1). (**b**) Depicts the TGF Beta signaling pathway (created by using biorender version 1).

gene via inhibition of cell proliferation and inducing apoptosis (Fig. 1b). It has been demonstrated that the escape of the tumor-suppressor effects of TGF-beta and resistance to TGF-beta-mediated growth inhibition contribute to CRC development. High levels of TGF-beta in primary CRC tumors are associated with advanced stages at time of diagnosis, increased likelihood of tumor recurrence, and overall decreased survival[9].

Despite the pivotal role of WNT and TGF-beta pathway alterations in CRC, the aberrations in these pathways were not well-described in young-onset CRC. Therefore, in this study, we aim to conduct a comprehensive molecular evaluation of WNT and TGF-beta signaling pathways in colorectal cancer across young-onset CRC and CRC developed in patients over 50 years of age. We also investigated other molecular characteristics of young-onset colorectal cancer, including tumor mutation burden and common driver oncogenes seen in CRC.

Methods

For this bioinformatics study, we used published individual patient-level genomic data of patients with colorectal cancer (CRC) from the 16 CRC datasets[10–23] included in the cBioPortal database[24]. The studies categorized under the bowel, colorectal adenocarcinoma, and colon adenocarcinoma headings were included, while one study specifically included patients with appendiceal adenocarcinoma was excluded. Additionally, due to lack of details regarding age, two large-scale pan-cancer datasets, MSK-IMPACT Clinical Sequencing Cohort and AACR-GENIE, were excluded from the study.

The WNT pathway alterations, including APC, AXIN1, AXIN2, GSK3B, and RNF43 mutations, were considered to define the WNT mutant CRC cohort. Similarly, TGF-beta pathway alterations were defined given gene alterations in the following: TGFBR2, TGFB2, TGFBRAP1, TGFBR1, TGFBR3, TGFB1I1, TGFBI, TGFB1, TGFBR3L, TGFB3, TGFA, SMAD1-9, BMPR2, BMPER, BMP3, BMP2K, BMP1, BMP5, BMP10, BMPR1A, BMP15, BMP7, BMP23, BMP4, BMP6, BMPR1B, BMP8B, BMP8A.

The baseline characteristics were expressed with frequency and percentages for continuous variables and medians and interquartile range for continuous variables. Custom groups were created according to age, presence or absence of WNT alterations and presence or absence of WNT alterations, and independent group comparisons were conducted. The presence of both WNT and TGF-beta alterations according to age (≤ 50 y versus > 50 years of age) were evaluated using Chi-square tests. The association between primary tumor distribution (colon versus rectal) and age was evaluated across patients with and without the WNT pathway and patients with and without TGF-beta pathway alterations. The effect of WNT and TGF-beta pathway alterations on the overall survival and survival after the metastatic stage was evaluated with Kaplan–Meier survival curves, and univariate hazard ratios with 95% confidence intervals (CI) were calculated. A type-I error level of 5% ($p < 0.05$) was considered the threshold limit for statistical significance.

Results

A total of sixteen studies, including 6532 samples, were retrieved from the studies. After the exclusion of patients with small bowel cancer (n = 15), cancer of unknown primary (n = 3), and CRC in situ, the remaining dataset comprised 6512 samples from 6286 patients (Table 1). The patients with young-onset CRC had a higher incidence

Clinical feature	n (%)
Age*	
≤ 50	476 (20.7)
> 50	1823 (79.3)
Detailed cancer type	
Colon cancer	2372 (36.4)
CRC	2289 (35.1)
Rectal cancer	1715 (26.3)
Other	136 (2.2)
Sex[#]	
Male	3220 (53)
Female	2854 (47)
Sample type[$]	
Primary	2938 (67.5)
Recurrence-metastasis	1404 (32.3)
Cell Line/PDX	8 (0.2)
Tumor site[&]	
Right colon	382 (50.5)
Left colon	224 (29.6)
Rectum	151 (19.9)

Table 1. Baseline patient characteristics of the study population. *N/A: 3987, [#]N/A: 212, [$]N/A: 2162, [&]N/A: 5529.

of rectum primaries (62.6 vs. 37.9%, $p < 0.001$) compared to patients with adult-onset CRC among cases with known primary tumor location. The patients with young-onset CRC were more frequently male compared to patients over 50 years of age (56.7 versus 49.3%, $p < 0.001$) (Table 2). The median tumor mutational burden (TMB) was significantly higher in patients with young-onset CRC (median: 6.17, IQR: 3.46–13.84) compared to patients > 50 years of age (median: 4.57, IQR: 2.97–8.8) ($p < 0.001$). Patients with young-onset CRC (≤ 50 years old) had higher rates of TP53 (68.1 versus 51.9, $p < 0.001$), LMNB1 (9 versus 1.2%, $p < 0.001$), while the rate of TTN (7.2 versus 25.7%, $p < 0.001$), KRTAP9-1 (0 versus 14.6%, $p < 0.001$), SYNE1 (4.5 versus 14.3%, $p < 0.001$), BRAF (4.1 versus 10.3%, $p < 0.001$) and FAT mutations (for FAT3 1.8 versus 8.2%, $p < 0.001$ and for FAT4 2 versus 10.1%, $p < 0.001$) were lower in patients with young-onset CRC (≤ 50 years old) compared to patients over 50 years of age. The frequency of KRAS mutations was numerically higher among younger patients, but this was not statistically significant (Table 2). The disease-free survival was significantly shorter in patients with

		≤ 50 Years	> 50 Years	*p* value
Median age (IQR)		44 (38–48)	68 (60–75)	< 0.001
Median mutation count		8 (5–17)	83 (9–151)	< 0.001
Median TMB (IQR)		6.17 (3.46–13.84)	4.57 (2.97–8.80)	< 0.001
Median FGA		0.14 (0.05–0.26)	0.20 (0.08–0.32)	< 0.001
Oncotree Code	COAD	94 (18.9)	496 (26.7)	< 0.001
	REaAD	311 (62.6)	611 (32.9)	
	COADREAD	75 (15.1)	697 (37.5)	
	MACR	15 (3)	55 (2.9)	
	SRCCR	2 (0.4)	0 (0)	
Sex*	Female	212 (42.9)	940 (50.6)	< 0.001
	Male	282 (57.1)	916 (49.4)	
KRAS Mutation	Present	171 (34.8)	560 (30.4)	0.071
	Absent	321 (65.2)	1283 (69.6)	
BRAF Mutation	Present	20 (4.1)	190 (10.3)	< 0.001
	Absent	472 (95.9)	1653 (89.7)	
TP53 Mutation	Present	335 (68.1)	957 (51.9)	< 0.001
	Absent	157 (31.9)	886 (48.1)	

Table 2. Comparison of the clinical features according to age groups. *N/A: 6 FGA: Fraction Genome Altered.

young-onset CRC (HR: 1.746, 95% CI 1.029–2.964, $p = 0.0112$). The overall survival was similar across young-onset CRC and patients > 50 years of age ($p = 0.455$).

The frequency of WNT pathway alterations was similar across young-onset CRC (≤ 50 years old) and CRC patients > 50 years of age (63.6% versus 60.3%, $p = 0.215$) (Table 3). While the rate of APC alterations was higher in young-onset CRC (60.9 versus 54.6%, $p = 0.016$), the rate of other mutations related to WNT pathway alterations was similar across two groups (AXIN1: 2.12 versus 2.33%, AXIN2: 4.68 versus 5%, GSK3B 1.24 versus 0.92%, RNF43 6.22 versus 7.70%; $p > 0.05$ for all). We observed that the WNT alterations were significantly more common in rectal cancers compared to colon cancers (76 versus 69.6%, $p < 0.001$) (Table 4). The median overall survival was similar in patients with or without WNT pathway alterations (59.9 versus 57.2 months, $p = 0.233$), while survival after the metastatic stage was longer in patients with WNT pathway alterations compared to patients without WNT pathway alterations (58.2 versus 41.7 months, $p < 0.001$) (Fig. 2).

	≤ 50 years old	> 50 years old
WNT alterations present	302 (63.6%)	1092 (60.3%)
WNT alterations absent	173 (36.4%)	718 (29.7%)
		P Value .196522
TGF alteration absent	390 (82.6%)	1301 (72%)
TGF alteration present	82 (17.4%)	507 (28%)
		P Value < 0.00001

Table 3. WNT and TGF Beta Alteration rates among patients ≤ 50 year-old or > 50 year-old.

	Colon	Rectal
WNT alterations present	1615 (69.6%)	1286 (76.0%)
WNT alterations absent	705 (30.4%)	407 (24.0%)
		P Value < 0.00001
TGF alterations absent	1767 (74.6%)	1367 (81.3%)
TGF alterations present	602 (25.4%)	314 (18.7%)
		P Value < 0.00001

Table 4. WNT and TGF beta alterations in colon versus rectal cancers.

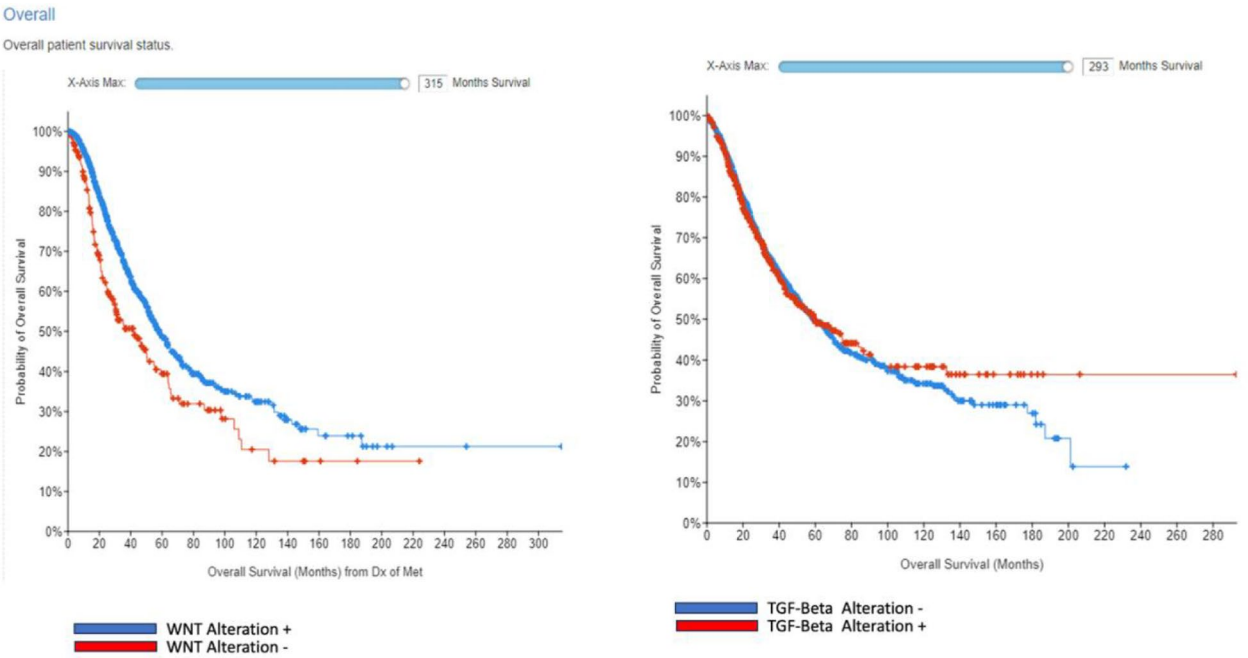

Figure 2. Demonstrates the overall survival curve of individuals with respect to WNT alteration presence or absence, and overall survival curve of individuals with respect to TGF Beta alteration presence or absence.

Mutations associated with the TGF-beta pathway were less common in patients with young-onset CRC compared to patients > 50 years of age (17.4 versus 28% $p < 0.001$) (Table 3). Notably, mutations associated with TGF-beta pathway alterations were more frequent in colon cancer compared to rectum (25.4% versus 18.7, $p < 0.001$) (Table 4). While progression-free survival was better in patients with TGF-beta pathway alterations (12.5 versus 10.7 months, $p = 0.012$), the overall survival (59.6 versus 58.9 months, $p = 0.896$) and survival after metastatic stage (49.7 versus 56.5 months, $p = 0.109$) were similar across the two groups (Fig. 2).

Discussion

The exact molecular underpinnings of young-onset CRC remain to be unclear. In this study, we identified significantly lower incidence of TGF-beta pathway alterations among patients with young-onset CRC as compared to patients with late-onset CRC. Our study did not reveal any difference in WNT pathway alterations. Notably, we identified better outcomes among patients with WNT pathway alterations regardless of age group. Rectal cancer appears to have more WNT dysregulation compared to colon cancer. To our knowledge, this is the first study demonstrating distinct molecular patterns with TGF-beta among younger individuals and the notable difference in WNT alterations in rectal cancer, which frequently affects younger individuals. Our study also identified an increased mean tumor mutation burden in younger patients than those in late-onset CRC. The results of our study also align with previously noted decreased BRAF V600E mutations in younger patients.

Young-onset CRC has a concerningly increasing trend in Western countries and is now a leading cause of cancer-related deaths among males ages 20–40[25]. At this time, the underlying reasons and molecular drivers of young-onset CRC have not been well defined[26]. Current evidence suggests that the vast majority of cases are linked to somatic genetic events among individuals with no known increased cancer risk or family history[26]. This indicates that there is increased environmental oncogenic exposure resulting in the development and accumulation of mutations early in life, triggering colonic carcinogenesis at young ages. Several environmental factors have been attributed to the development of young-onset CRC, including variation in gut microbiome, increased intake of processed meat, food, and sugary beverages, increased body mass index, excessive alcohol consumption, and a sedentary lifestyle[27]. Notably, most of these risk factors, particularly the gut microbiome, are linked to inflammation, which is a known risk factor for colonic carcinogenesis. Perhaps increased inflammation accelerates colonic carcinogenesis and results in early-onset colorectal cancer[28].

Molecular features of young-onset CRC have been of interest to research, and several studies have investigated potential distinct genetic alterations seen in this population. Notably, while some studies indicate that KRAS mutation is more common among patients with young onset CRC[29], more recent studies suggest that a lower incidence of KRAS mutations is among younger population[30]. In our study, we identified similar rates of KRAS mutations among patients with young-onset and adult-onset CRC. Notably, the investigators noted an increased incidence of TP53 and β-catenin mutations among young adults[30]. However, it is important to note that there are several other proteins involved in the Wnt pathway beyond the β-catenin, and our comprehensive mutation analyses did not reveal differences in genomic alterations involved in the Wnt signaling. To date, several studies indicate patients with young onset CRC are less likely to have BRAF V600E mutation compared to those with adult-onset CRC[31]. Our study findings also align with growing evidence on distinct patterns of BRAF mutations in younger adults, and we noted a lower frequency of BRAF mutations among young adults. Expectedly younger and more likely to have microsatellite instability-high disease, given lynch syndrome is linked with young onset cancer[32]. Overall, these data show distinct patterns of molecular alterations seen in young-onset CRC, some of which are actionable and indicate the importance of performing next-generation sequencing for patients with CRC, particularly for those with young onset disease.

WNT pathway alterations are one of the most common oncogenic events for colonic carcinogenesis[33]. APC, a tumor suppressor protein that regulates functions of β-catenin, is frequently mutated among alterations and can be seen in up to 80% of patients with metastatic colon cancer[34]. Germline mutations in APC result in Familial Adenomatous Polyposis syndrome and cause early-onset colorectal cancer[35]. Several other WNT pathway alterations including APC, AXIN1, AXIN2, GSK3B have also been associated with colorectal cancer[32]. In our study, we did not identify any significant difference between young-onset and late-onset CRC groups, indicating canonical WNT pathway alterations are also frequent founder events in the majority of patients with young-onset CRC. Notably, patients with rectal cancer were found to have more WNT alterations than patients with colon cancer, and this finding should be further investigated in other datasets. Interestingly, our study also suggested patients with WNT alterations may be associated with improved outcomes. This may be partially due to the lower incidence of BRAF V600E among patients with APC alterations (consensus molecular subgroup CMS1 vs CMS2), resulting in more favorable outcomes[36].

TGF-beta pathway alterations are another common oncogenic mechanism that have been linked to colorectal cancer development[37]. In fact, these alterations have been classified in the CMS4 subgroup, which is enriched by TGF-beta dysregulation and increased epithelial-mesenchymal transformation. TGF-beta pathway dysregulation can serve both as a tumor suppressor and pro-oncogene, depending on the biological evolution of cancer[38,39]. In our study, we identified a lower incidence of TGF-beta pathway alterations among patients with young-onset CRC as compared to those with late-onset CRC. A landmark study identified an increased incidence of common TGF-beta mutations among patients with right-sided colon cancer than those with left-sided cancer[40]. This finding aligns with our results, as patients with young-onset CRC were more likely to have left-sided colon and rectal cancer compared to patients with late-onset CRC. Further clinical and translational studies are warranted to better understand this distinct molecular signature among patients with young-onset CRC.

There are several limitations of this study, including the retrospective nature of the study, potential selection bias that may originate from CRC datasets included in the cBioPortal, lack of detailed clinical data and treatment history, and limited survival data. The strength of our study includes the ability to evaluate comprehensive

molecular data in a relatively large cohort of patients with early-onset colorectal cancer. Further prospective studies are warranted to validate our findings in larger cohorts.

Conclusion

In this large database study, we identified distinct molecular alterations among patients with young-onset CRC. Altered TGF-beta pathways appear to be seen less frequently among younger adults. Although it was slight, a significant difference in tumor mutation burden was noted, with younger patients demonstrating a relatively increased mutation burden. Our study did not reveal any difference in WNT pathway alterations between patients with young and late-onset CRC. Our results provide further insight into biological differences between young and adult-onset CRC, which sheds light on the unmet need for drug development in these molecular pathways affecting young individuals. Prospective clinical and translational studies are warranted to better understand these molecular variations seen among patients presenting with early-onset CRC, which may advance our understanding and help us develop preventive and therapeutic interventions.

Data availability

Data is available within the article and also available upon request from corresponding author.

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Author contributions

Author I.H.S. was primarily responsible for design and overseeing of the study. M.F., D.G., and I.H.S. wrote the manuscript text with contributions from C.G., E.N., R.G., S.C., M.P.S., T.M., A.S., and A.S. D.G. was primarily responsible for data analysis with assistance by I.H.S. and M.F. T.S created Figs. 1a and 1b. M.F., D.G., and I.H.S. created Tables 1–4. All listed authors provided edits and approved the submitted version.

Competing interests

The authors declare no competing interests.

Additional information

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