Original Article

TNFRSF10C copy number variation is associated with metastatic colorectal cancer

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Background: Genetic markers for distant metastatic disease in patients with colorectal cancer (CRC) are not well defined. Identification of genetic alterations associated with metastatic CRC could help to guide systemic and local treatment strategies. We evaluated the association of tumor necrosis factor receptor superfamily member 10C (*TNFRSF10C*) copy number variation (CNV) with distant metastatic disease in patients with CRC using The Cancer Genome Atlas (TCGA).

Methods: Genetic sequencing data and clinical characteristics were obtained from TCGA for all available patients with CRC. There were 515 CRC patient samples with CNV and clinical outcome data, including a subset of 144 rectal adenocarcinoma patient samples. Using the TCGA CRC dataset, CNV of *TNFRSF10C* was evaluated for association with distant metastatic disease (M1 *vs*. M0). Multivariate logistic regression analysis with odds ratio (OR) using a 95% confidence interval (CI) was performed adjusting for age, T stage, N stage, adjuvant chemotherapy, gender, microsatellite instability (MSI), location, and surgical margin status.

Results: *TNFRSF10C* CNV in patients with CRC was associated with distant metastatic disease [OR 4.81 (95% CI, 2.13–10.85) P<0.001] and positive lymph nodes [OR 18.83 (95% CI, 8.42–42.09)]; P<0.001) but not MSI (OR P=0.799). On multivariate analysis, after adjusting for pathologic T stage, N stage, adjuvant chemotherapy, gender, and MSI, *TNFRSF10C* CNV remained significantly associated with distant metastatic disease (OR P=0.018). Subset analysis revealed that *TNFRSF10C* CNV was also significantly associated with distant metastatic disease in patients with rectal adenocarcinoma (OR P=0.016).

Conclusions: *TNFRSF10C* CNV in patients with CRC is associated with distant metastatic disease. With further validation, such genetic profiles could be used clinically to support optimal systemic treatment strategies versus more aggressive local therapies in patients with CRC, including radiation therapy for rectal adenocarcinoma.

Keywords: Biomarker; colorectal cancer (CRC); rectal cancer; copy number variation (CNV); copy number aberration; genetic marker

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Introduction

Colorectal cancer (CRC) is the third leading cause of cancer-related death in the United States in both men and women, and approximately 20% of all current patients with CRC have distant metastatic disease (1) Despite advances in screening and treatment, the 5-year overall survival for patients with CRC is still dismal (1). Genes associated with the presence and development of CRC and markers for drug response have been characterized (2-4), but genetic markers associated with metastatic disease in CRC are not well defined. Treatment strategies for CRC are dependent upon stage and location of the primary tumor, and may use a combination of surgical resection, chemotherapy, and radiation therapy. In particular, radiation therapy improves local control and overall survival in patients with rectal adenocarcinoma (5). Copy number variations (CNVs) have been used to determine prognosis and subsequent treatment profile for a number of cancers, e.g., *MYCN* amplification for neuroblastoma (6). Comparisons between CNV of genes in primary CRC tumors and their matched metastatic disease sites are well documented, but less is known about how CNV of genes in CRC primary tumors differs between those associated with localized disease compared with those associated with distant metastatic disease (7-12).

Prior studies have shown a role for TNF-related apoptosis inducing ligand (TRAIL) dysregulation at multiple cancer sites, and a smaller study showed evidence of down regulation of tumor necrosis factor receptor superfamily member 10C (*TNFRSF10C)* at the sites of metastatic disease in CRC (13-16). TNFRSF10C, also known as decoy receptor-1 (DcR1) and TRAIL-R3, is a decoy TRAIL receptor, which functions as an antagonistic receptor that protects cells from TRAIL-induced apoptosis (17). *TNFRSF10C* expression is often down regulated in cancer (13-15), and loss of *TNFRSF10C* sensitizes cells to TRAIL-induced apoptosis (18). Indeed, TRAIL genes are prognostic for response to chemotherapy and overall survival in patients with CRC, and moreover are prognostic for outcome in patients with other cancers, including glioblastoma multiforme and breast cancer (19-24). Differences in TRAIL expression in cancers compared with normal cells have led to clinical trials targeting TRAIL-induced apoptosis in CRC, but the genetic profiles of patients were not used as part of the selection criteria (25-29).

Tri-modality treatment with surgery, chemotherapy, and radiation therapy represents the standard of care in the majority of patients with stage II-III rectal adenocarcinoma. The current PROSPECT clinical trial is examining the possible omission of radiation therapy in select patients with rectal adenocarcinoma and instead using more aggressive chemotherapy strategies (30). Identifying genetic markers that can discriminate whether patients have a propensity for localized *vs.* metastatic disease could lead to the individualization of treatment for patients with rectal adenocarcinoma and help to identify those patients who may be more likely to benefit from more aggressive chemotherapeutic strategies.

In this study, we assessed the association of *TNFRSF10C* CNV with distant metastatic disease in CRC using a cohort of 515 patients from The Cancer Genome Atlas (TCGA).

Methods

Patient data

A cohort of 515 samples taken from primary tumor specimen was selected from the TCGA database in April 2014 based on availability of both metastatic staging and copy number data. A subset of 144 samples with rectal primary and CNV data was separately analyzed. The results here are in part based upon data generated by the TCGA Research Network (http://cancergenome.nih.gov/) established by the NCI and NHGRI.

Clinicopathological data

Data on age, sex, staging, and race/ethnicity was collected from clinical information on the TCGA data portal. Pathologic findings of tumor size, tumor location, resection margins, lymph node status and metastatic status at diagnosis were also available through the TCGA data portal.

CNV analysis

The TCGA level 3 CNV data was extracted for colon and rectal adenocarcinoma from TCGA data portal. TCGA level 3 CNV (Affymetrix Genome-Wide SNP Array 6.0) was processed and normalized per sample. The mean copy number estimates of segments overlapping the whole genome were obtained and used for the analysis. Genomic identification of significant targets in cancer (GISTIC) algorithm mean cut-offs were used to categorize the gene. Copy numbers ≥1 or ≤–1 were defined as presence of CNV.

Statistical analysis

In the CRC set, univariate association of TNFRSF10C CNV with covariates was examined with chi-square test or Fisher's exact test, where appropriate. Univariate analysis of metastatic disease (M1 *vs.* M0) with predictors and covariates was carried out with a logistic regression model. Multivariable analysis of metastatic disease (M1 *vs.* M0) was conducted with a logistic regression model by entering all variables in the model and using a backward variable selection method with an alpha level of removal of 0.1. TNFRSF10C CNV, chemotherapy, N stage, and T stage were forced in the model.

For the rectal subset, univariate association of TNFRSF10C CNV with covariates was examined with chi-square test or Fisher's exact test, where appropriate. Univariate analysis of metastatic disease (M1 *vs.* M0) with the predictor and covariates was carried out with a logistic regression model. Multivariable analysis of metastatic disease (M1 *vs.* M0) was conducted with a logistic regression model by entering all variables in the model and using a backward variable selection method with an alpha level of removal of 0.1. TNFRSF10C CNV, N stage, and T stage were forced in the model. All analyses were done using SAS 9.3 (SAS Institute, Inc., Cary, North Carolina, USA) with a significant level of 0.05.

Upon determining significance between TNFRSF10C CNV and distant metastatic disease in both the colorectal cohort and rectal subset, TNFRSF10C CNV data was further queried to determine if the CNV was a gain or loss, and overwhelmingly the CNV was a homozygous deletion indicating copy number loss.

Results

The CRC copy number analysis cohort (*Table 1*) consisted of 515 patients with the diagnosis of CRC (270 male and 245 female). The median age at diagnosis was 68 years (range, 31–90 years). The rectal subset for copy number analysis (*Table 2*) contained 144 patients (77 male and 67 female) with a median age at diagnosis of 65 years (range, 31–90 years).

Pathological characteristics

In the CRC copy number analysis cohort, distant metastatic disease was diagnosed in 72 (14%) patients, and 211 (41%) patients had positive nodal disease. In the rectal subset, 22 (15%) patients had distant metastatic disease and 66 (46%) patients had positive nodal disease.

Table 1 Sample characteristics for colorectal patients with copy number analysis (n=515)

Characteristic	Number (%)*
Gender	
Male	270 (52.43)
Female	245 (47.57)
Race/ethnicity	
White	232 (84.36)
Non-white†	43 (15.64)
Missing	240
Age in years (mean ± standard deviation)	66.47±12.53
Adjuvant chemotherapy	
Yes	130 (36.01)
No	231 (63.99)
Missing	154
Pathologic M stage	
M0	443 (86.02)
M1	72 (13.98)
Pathologic N stage	
N0	303 (58.95)
N1	120 (23.35)
N2	91 (17.70)
Missing	1
Pathologic T stage	
T0	1 (0.19)
T1	16 (3.11)
T2	93 (18.06)
T3	359 (69.71)
T4	46 (8.93)
Microsatellite instability	
MSI	149 (29.45)
MSS	357 (70.55)
Missing	9
Location	
Colon	370 (71.98)
Rectum	144 (28.02)
Missing	1
Resection margins	
Positive††	40 (9.32)
Negative	389 (90.68)
Missing	86

*, percentages calculated did not include missing data; †, non-white included Asian, Hispanic, Black, and African-American; ††, positive margin refers to microscopic (R1) or macroscopic (R2) residual disease. MSI, microsatellite instability; MSS, microsatellite stability.

Table 2 Sample characteristics for rectal subset with copy number analysis (n=144)

Characteristic	Number (%)*
Gender	
Male	77 (53.47)
Female	67 (46.53)
Race/ethnicity	
White	63 (92.65)
Non-white†	5 (7.35)
Missing	76
Age in years (mean ± standard deviation)	64.33±11.76
Adjuvant chemotherapy	
Yes	38 (46.34)
No	44 (53.66)
Missing	62
Pathologic M stage	
M0	122 (84.72)
M1	22 (15.28)
Pathologic N stage	
N0	78 (54.17)
N1	40 (27.78)
N2	26 (18.05)
Pathologic T stage	
T1	8 (5.55)
T2	27 (18.75)
T3	98 (68.06)
T4	11 (7.64)
Microsatellite instability	
MSI	19 (13.29)
MSS	124 (86.71)
Missing	1
Resection margins	
Positive††	13 (10.24)
Negative	114 (89.76)
Missing	17

*, percentages calculated did not include missing data; †, non-white included Asian, Hispanic, Black, and African-American; ††, positive margin refers to microscopic (R1) or macroscopic (R2) residual disease. MSI, microsatellite instability; MSS, microsatellite stability.

Genetic analysis for all patients

There were 27 samples that had CNV at TNFRSF10C, and the samples displayed decreased copy number through homozygous deletions. On univariate analysis, *TNFRSF10* CNV demonstrated a statistically significant association with distant metastatic disease (P<0.001), positive nodal disease (P=0.005) and positive resection margins (P<0.001). There was no association found between *TNFRSF10C* CNV with microsatellite instability (MSI), location, or T stage (*Table 3*).

On univariate analysis for metastatic disease (*Table 4*), presence of distant metastatic disease was found to be associated with presence of *TNFRSF10C* CNV [odds ratio (OR) 4.81; 95% confidence interval (CI), 2.13–10.85; P<0.001], N1 or N2 nodal disease [OR 18.83 (95% CI, 8.42–42.09); P<0.001], T3 or T4 advanced local disease [OR 11.18 (95% CI, 2.70–46.36); P<0.001], positive resection margins [OR 90.14 (95% CI, 34.35–236.52); P<0.001], and use of adjuvant chemotherapy [OR 4.90 (95% CI, 2.54–9.44); P<0.001]. On multivariate analysis (*Table 4*), presence of *TNFRSF10C* CNV remained associated with presence of distant metastatic disease [OR 4.63 (95% CI, 1.31–16.43); P=0.018], in addition to N1 or N2 nodal disease [OR 14.45 (95% CI, 4.55–45.83); P<0.001]. Race/ethnicity, location, and resection margins were dropped from the multivariate model.

Subset analysis of rectal cancer patients

On univariate analysis for presence of metastatic disease in the rectal subset (*Table 5*), distant metastatic disease was significantly associated with TNFRSF10C CNV [OR 5.69 (95% CI, 1.56–20.69); P=0.008], N1 or N2 nodal disease [OR 35.93 (95% CI, 4.67–276.13); P<0.001] and positive resection margins [OR 84.07 (95% CI, 15.52–455.42); P<0.001]. Adjuvant chemotherapy, MSI and pathologic T stage were not associated with presence of distant metastatic disease. On multivariate analysis including TNFRSF10C CNV analysis, T stage, and N stage in the logistic regression model, presence of metastatic disease remained associated with TNFRSF10C alteration [OR 10.69 (95% CI, 1.56–73.15); P=0.016] and N1 or N2 nodal disease [OR 38.02 (95% CI, 4.38–329.72); P<0.001]. Adjuvant chemotherapy, gender, MSI, race/ethnicity, and resection margins were removed from the model.

Discussion

In this study, we found that *TNFRSF10C* CNV was

Table 3 Univariate association for colorectal patients with TNFRSF10C CNV (n=515)

Characteristic	CNV N=27 (%)	No CNV N=488 (%)	P value*
Gender			
Male	17 (6.3)	253 (93.7)	0.260
Female	10 (4.08)	235 (95.92)	
Race/ethnicity			
White	9 (3.88)	223 (96.12)	0.684
Non-white	2 (4.65)	41 (95.35)	
Adjuvant chemotherapy			
Yes	10 (7.69)	120 (92.31)	0.045
No	7 (3.03)	224 (96.97)	
Pathologic N stage			
N1 or N2	18 (8.53)	193 (91.47)	0.005
N0	9 (2.97)	294 (97.03)	
Pathologic T stage			
T3 or T4	21 (5.19)	384 (94.81)	0.894
T1 or T2	6 (5.5)	103 (94.5)	
Pathologic M stage			
M1	11 (15.28)	61 (84.72)	<0.001
M0	16 (3.61)	427 (96.39)	
Microsatellite instability			
MSI	8 (5.37)	141 (94.63)	0.879
MSS	18 (5.04)	339 (94.96)	
Location			
Colon	16 (4.32)	354 (95.68)	0.130
Rectum	11 (7.64)	133 (92.36)	
Resection margins			
Positive†	8 [20]	32 [80]	<0.001
Negative	15 (3.86)	374 (96.14)	

*, the P value is calculated by chi-square test or fisher's exact test for categorical covariates, where appropriate; †, positive margins refers to microscopic (R1) or macroscopic (R2) residual disease. TNFRSF10C, tumor necrosis factor receptor superfamily member 10C; CNV, copy number variation; MSI, microsatellite instability; MSS, microsatellite stability.

independently associated with distant metastatic disease in CRC and the rectal subset from an analysis of data from 515 patients utilizing TCGA. We confirmed our findings on multivariate analysis, taking into account age, T stage, N stage, adjuvant chemotherapy, gender, MSI, location, and surgical margin status. Our findings provide evidence that *TNFRSF10C* CNV is significantly associated with distant metastatic disease in patients with all forms of CRC

Table 4 Univariate and multivariate analysis for presence of distant metastatic disease (M1 *vs.* M0)

Characteristic	Univariate analysis		Multivariate analysis*	
	OR (95% CI)	P value	OR (95% CI)	P value
TNFRSF10C copy number				
Variation	4.81 (2.13–10.85)	<0.001	4.63 (1.31–16.43)	0.018
No variation	[1]		[1]	
Gender				
Male	1.16 (0.70–1.91)	0.567	1.96 (0.96–4.00)	0.066
Female	[1]		[1]	
Adjuvant chemotherapy				
Yes	4.90 (2.54–9.44)	<0.001	1.74 (0.76–3.95)	0.189
No	[1]		[1]	
AJCC pathologic N stage				
N1 or N2	18.83 (8.42–42.09)	<0.001	14.45 (4.55–45.83)	<0.001
N0	[1]		[1]	
AJCC pathologic T stage				
T3 or T4	11.18 (2.70–46.36)	<0.001	4.30 (0.85–21.69)	0.077
T1 or T2	[1]		[1]	
Microsatellite instability				
MSI	0.93 (0.53–1.62)	0.799	2.22 (0.99–4.96)	0.052
MSS	[1]		[1]	
Race/ethnicity				
White	1.17 (0.43–3.21)	0.757	†	
Non-white	[1]			
Location				
Colon	0.87 (0.50–1.49)	0.605	†	
Rectum	[1]			
Resection margins				
Positive††	90.14 (34.35–236.52)	<0.001	†	
Negative	[1]			

*, 356 of 515 observations were used in the multivariable logistic model. Backward selection with an alpha level of removal of 0.1 was used. TNFRSF10C copy number alteration, chemotherapy, N stage and T stage were forced in the model. †, variables dropped from the model; ††, positive margin refers to microscopic (R1) or macroscopic (R2) residual disease. CI, confidence interval; OR, odds ratio; MSI, microsatellite instability; MSS, microsatellite stability; TNFRSF10C, tumor necrosis factor receptor superfamily member 10C.

Table 5 Univariate and multivariate analysis for presence of distant metastatic disease (M1 *vs.* M0) in rectal subset

Characteristic	Univariate analysis		Multivariate analysis*	
	OR (95% CI)	OR P value	OR (95% CI)	P value
TNFRSF10C copy number				
Variation	5.69 (1.56–20.69)	0.008	10.69 (1.56–73.15)	0.016
No variation	[1]		[1]	
Gender				
Male	1.64 (0.64–4.19)	0.302	†	
Female	[1]			
Adjuvant chemotherapy				
Yes	3.10 (0.87–11.06)	0.081	†	
No	[1]			
AJCC pathologic N stage				
N1 or N2	35.93 (4.67–276.13)	<0.001	38.02 (4.38–329.72)	<0.001
N0	[1]		[1]	
AJCC pathologic T stage				
T3 or T4	3.71 (0.82–16.74)	0.088	1.83 (0.19–17.56)	0.603
T1 or T2	[1]		[1]	
Microsatellite instability				
MSI	2.25 (0.72–7.04)	0.165	†	
MSS	[1]			
Race/ethnicity				
White	0.67 (0.07–6.66)	0.73	†	
Non-white	[1]			
Resection margins				
Positive††	84.07 (15.52–455.42)	<0.001	†	
Negative	[1]			

*, of 144, 144 observations were used in the multivariable logistic model. Backward selection with an alpha level of removal of 0.1 was used. TNFRSF10C copy change, T stage, and N stage were forced in the model. †, variables dropped from the model; ††, positive margin refers to microscopic (R1) or macroscopic (R2) residual disease. CI, confidence interval; OR, odds ratio; MSI, microsatellite instability; MSS, microsatellite stability; TNFRSF10C, tumor necrosis factor receptor superfamily member 10C.

and in patients with rectal cancer. Additionally, these data suggest that CNV in *TNFRSF10C* may be a useful genetic marker to personalize treatment for patients with CRC, and potentially identify those patients who may benefit from more aggressive systemic treatment strategies.

A recent large-scale analysis of TCGA by Lee *et al.* did not find any evidence of a significant genetic association with distant metastatic disease when incorporating multiple genetic markers (mutations, CNV, gene expression, and methylation status) into the analysis (8). Our study differs in the finding of a CNV of a unique gene independently associated with distant metastatic disease utilizing a larger database with more samples having distant metastatic disease. In the Macartney-Coxson *et al.* study of 30 patients with CRC, low *TNFRSF10C* expression was associated with the development of extrahepatic metastases (13). Consistent with these findings, the instances of *TNFRSF10C* CNV in our cohort were overwhelmingly homozygous deletions, and therefore associated with downregulation of the gene. *TNFRSF10C* CNV is associated with more aggressive disease in CRC as demonstrated by its association with distant metastases and nodal disease in our cohort.

The current cohort contained many samples of both colectomy and metastatic disease thereby allowing

correlative analysis with more statistical power. Distant metastatic disease is associated with nodal disease, and trends with advanced T stage. Another factor that also plays a role in the development of distant metastatic disease is the molecular pathway of tumorigenesis. Hereditary non-polyposis CRC is associated with left colon primary tumors with a lower propensity of forming metastases, as well as being associated with MSI (31) Several studies have indicated different molecular and clinical features amongst different locations in the colon (2,32,33), and for the aforementioned reasons we controlled for MSI when examining any association of *TNFRSF10C* CNV with distant metastatic disease. Although there was an expected trend between distant metastatic disease in the CRC cohort and microsatellite stability (MSS) (P=0.052) on multivariate analysis, *TNFRSF10C* CNV was not found to be associated with MSI/MSS on univariate analysis (P=0.879), and moreover, *TNFRSF10C* was independently associated with distant metastatic disease (P=0.018) on multivariate analysis. Taken together, these findings suggest that the relationship between *TNFRSF10C* CNV and distant metastatic disease is not dependent upon an association with the molecular differences between right-sided and left-sided primary tumors.

Variations in molecular expression and somatic changes have been reported between colon and rectal cancers (34,35). Due to these differences, subset analysis was performed in rectal adenocarcinoma samples. Rectal adenocarcinoma subset analysis confirmed that *TNFRSF10C* CNV was independently associated with distant metastases. Therefore, the reported changes between rectal and colon primaries do not seem to affect the association of *TNFRSF10C* CNV and distant metastases in rectal primary patients. Significantly, rectal and colon cancers have differences in treatment strategies. Radiation therapy is often used in rectal adenocarcinomas due to a higher incidence of local recurrence in rectal adenocarcinoma compared with CRC (36). Although local recurrence may be a main target in therapy for locally advanced tumors, there must also be consideration for the development of metastases as aggressive local treatment would be of less benefit. Multiple studies have shown that the number of lymph nodes sampled during surgery for CRC is correlated with prognosis in stage II CRC, thus implicating that further treatment may prevent a reservoir for the spread of cancer (37,38). With increasing evidence of spread of tumor in the early stages of CRC, the use of another indicator like *TNFRSF10C* CNV may be useful in guiding therapy toward a more aggressive regimen focused on preventing the spread of tumor. After surgery, rectal adenocarcinoma treatment will usually focus on a systemic therapy versus localized therapy, thus the use of a clinical marker associated with distant metastatic disease could help to influence treatment in rectal cancer to favor systemic therapy versus radiation therapy. The use of *TNFRSF10C* as a molecular marker to influence therapy will depend upon future studies having a longitudinal design thereby allowing more association with development of advanced disease with distant metastases.

We acknowledge that this study does have limitations in addition to the retrospective design. The data was obtained from patients who had resection of primary tumor, thereby not involving advanced, unresectable disease in the analysis. Some of the clinical information, e.g., race/ethnicity of the patients, was not recorded for 47% of the patients, and some CNV may be associated more with different nationalities/backgrounds (39). The retrospective analysis only allowed the ability to compare genetic alterations with the presence of metastatic disease. The inability to have a prospective component after genetic analysis limits the application of the findings and prevents the determination of factors associated with development of distant metastases.

Although other studies have shown somatic changes and CNV that characterize the genomes of multiple cancer types, no previous study has associated the CNV of *TNFRSF10C* at the primary site with distant metastatic disease. The association could influence treatment strategies, as well as potentially serve as a marker for targeted molecular therapy.

Conclusions

In conclusion, our cohort displayed a statistically significant association between *TNFRSF10C* CNV and distant metastatic disease in CRC and rectal adenocarcinoma. With further validation in longitudinal studies, *TNFRSF10C* CNV may be used clinically to support optimal systemic treatment strategies versus more aggressive local therapies in patients with CRC, including radiation therapy for rectal adenocarcinoma.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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