Differential Immune Signatures in the Tumor Microenvironment are Associated with Colorectal Cancer Racial Disparities: A Cohort Study of Biorepository Data

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Abstract

Background: Disparities in colorectal cancer outcomes may be due to a more aggressive phenotype in African American patients in the setting of a decreased tumor immunity, though the precise mechanism for this result has not been well elucidated. To explore the molecular factors underlying colorectal cancer disparities, we compared the immunogenomic signatures of colorectal cancer from African American and European American patients.

Methods: We identified all colorectal cancer patients from the publicly available Cancer Genome Atlas for whom race and survival data are available. Immunophenotype signatures were established for African American and European American patients. Comparisons were made regarding survival and a multivariable linear regression model was created to determine the association of immune cellular components with race. Differential gene expression was also assessed.

Results: Of the 254 patients identified, 58 (23%) were African American and 196 (77%) were European American. African American patients had a decreased progression free survival ($p=0.04$). Tumors from African American patients displayed a reduced fraction of macrophages and CD8⁺ T cells and an increased fraction of B cells compared with tumors from European Americans. Differences persisted when controlling for sex, age and disease stage. Immunostimulatory and immunoinhibitory gene profiles including MHC expression differed by race.

Conclusions: Differences in the tumor immune microenvironment of African American as compared to European American colorectal cancer specimens may play a role in the survival differences between the groups. These differences may provide targeted therapeutic opportunities.

Background

Colorectal cancer (CRC) is the third most common malignancy, and the second leading cause of cancer death in the United States.(1) Compared to European Americans (EAs), blacks with African ancestry (AAs) have a substantially higher (30–50%) CRC mortality rate, marked by both higher incidence and lower survival rates.(2) Socioeconomic factors and absence of preventive medical care likely contribute to the heightened incidence, reduced early detection and delayed treatment. However, CRC racial health disparity remains profound despite improved CRC screening in AA patients.(3–8)

Growing evidence has demonstrated that CRC in AAs has unfavorable tumor biology. A 2018 study by Sineshaw and colleagues using the National Cancer Database found that while access to care and tumor stage accounted for three quarters of the AA-EA survival disparity in patients under 65, fully 25% of the survival difference remains unexplained by these factors suggesting that tumor biology and immune factors may play a role in this disparity.(9) For instance, variations exist in AA patients, specifically in mutations of the mismatch repair genes, PIK3CA and the *p53* tumor suppressor gene.(10, 11) Recent evidence in breast and prostate cancer has implicated underlying racial differences in inflammation and immunity as key drivers of the respective cancer disparities.(12, 13) In addition, gene expression profiling

of CRC patients determined that prominent differences were observed in pathways related to inflammatory and cell-mediated immune response between AAs and EAs.(11) A recent study demonstrated decreased anti-tumoral cytotoxic immunity suggested by reduced Granzyme B + TIL population among AA patients.(4) Thus, AA CRC patients have altered immunity, although the underlying mechanism has not been determined.

The Cancer Genome Atlas (TCGA) and large CRC molecular profiling analyses have defined distinct CRC molecular subtypes related to anatomy and tumoral immunity.(14–17) In parallel, landmark studies have established the prognostic importance of the quantity and quality of the CRC tumor infiltrating lymphocyte (TIL).(18, 19) Novel secondary analyses have used TCGA to identify specific immunogenomic gene signatures to describe the tumor immune microenvironment based on unique gene signatures identifying specific cell types.(20, 21) CRC immunogenomic subtypes have effectively correlated with long-term survival as well as predicted response to immune checkpoint inhibitors.(20) To explore molecular aspects underlying CRC cancer disparities, we compared the immunogenomic signatures of CRC from AA and EA patients.

Methods

Patients/Data Sources

TCGA data for CRC previously analyzed by Thorsson and colleagues were made publicly available through the National Cancer Institute Genomic Data Commons.(21) These data were then integrated with genomic and clinical data available in the cBioportal for Cancer Genomics, an online platform designed to facilitate access to complex cancer genomics data.(22) We identified all CRC patients from TCGA with immunophenotype data for whom race and survival data were available.

Characterization of immunophenotype - TCGA

The leukocyte composition associated with each CRC sample within TCGA was previously characterized as an immune cellular fraction using CIBERSORT, a method of estimating proportions of cell types from gene expression profiles.(21, 23) Cell types were considered as an immune cellular fraction and compared between AA and EA CRC patients. Immune cell subsets are aggregated into nine classes with respect to the cytokine network, including CD8 T cells, CD4 T cells (naïve, memory, resting and activated), B cells (naïve and memory), NK cells (resting and activated), macrophage (M0, M1, M2), dendritic cells (resting, activated), mast cells (resting and activated), neutrophils and eosinophils; “Aggregate 2” described in the Supplementary Materials of Thorsson et al.(21) Immune cellular fraction was then modeled using race, sex, disease stage and age, which was presented as a dichotomous variable above and below 55 years. Specific lymphocyte and macrophage subtypes were then estimated for AA and EA patients. Lymphocyte and macrophage cellular fractions were also modeled using race, sex, disease stage and age.

Characterization of immune gene expressions - TCGA

Gene expressions for immuno-inhibitors and immuno-stimulators were obtained from the cbiportal database (<http://www.cbiportal.org/>) and compared between EA and AA CRC patients. Specifically, gene expressions were utilized in the form of z-scores, the relative expression of an individual gene in a tumor sample compared to the gene's expression distribution in a reference population of samples, where the reference population is defined as all samples that are diploid for that gene.(24) Major histocompatibility complex (MHC) gene expression level was also compared.

Statistical analysis

Kaplan-Meier curves were used to demonstrate overall and progression free survival.(25) Survival curves were compared using the log-rank test. A multivariable linear regression model was created to determine the association of immune cellular fraction components with race, sex, age and disease stage used as covariates. All analyses were conducted using R software version 3.5.3. Throughout all analyses, statistical significance was as determined by a criterion of $p < 0.05$. The Institutional Review Board of the Medical University of South Carolina approved this analysis.

Results

Clinical CRC patient characteristics

Of the 427 patients with colon cancer from TCGA immunogenomics data set, we identified 254 patients; 58 AA (23%) and 196 EA (77%) with racial and survival data available. Their demographic characteristics are outlined in Table 1. No differences existed with respect to gender or disease stage. In the CRC TCGA cohort, no differences in overall survival were observed between AA and EA patients (Fig. 1A). However, progression-free survival for AA patients was decreased as compared to EA patients (log-rank, $p = 0.04$) (Fig. 1B). In addition, median progression-free survival for AA patients is 1678 days while median progression-free survival for EA patients was not reached.

Table 1
Demographics of African and European American patients.

	Overall (N = 254)	European American (N = 196)	African American (N = 58)	p-value
AGE				0.04
Mean (SD)	64.9 (13.5)	65.9 (13.2)	61.5 (14.1)	
Median	67.0	68.0	61.0	
[Min, Max]	[31.0, 90.0]	[34.0, 90.0]	[31.0, 90.0]	
GENDER				0.55
Female	126 (49.6%)	95 (48.5%)	31 (53.4%)	
Male	128 (50.4%)	101 (51.5%)	27 (46.6%)	
STAGE				0.60
STAGE I	42 (16.5%)	34 (17.3%)	8 (13.8%)	
STAGE II	94 (37.0%)	75 (38.3%)	19 (32.8%)	
STAGE III	81 (31.9%)	61 (31.1%)	20 (34.5%)	
STAGE IV	37 (14.6%)	26 (13.3%)	11 (19.0%)	

Racial differences in the CRC immune microenvironment

Using the analytic strategy described by Thorsson(21), immune populations were identified in tumors from both AA and EA CRC patients. This analysis identified significant differences in gene expression associated with specific immune cell populations that persisted when controlling for sex, age and disease stage. Compared with tumors from EA patients, tumors from AA patients showed a greater proportion of B cells ($p < 0.01$) and a decreased proportion of macrophages ($p < 0.01$) and CD8 T cells ($p = 0.03$) as compared to EA patients (Fig. 2 and Supplemental Table 1). As differences were identified for CD8 T cells, B cells, and macrophages, subsets of these cell types were further analyzed for association with race (Table 2). AA patient tumors have more memory B ($p < 0.01$) and plasma cells ($p < 0.01$) compared with EA patient tumors. In addition to fewer macrophages, pro-inflammatory macrophages with an M1 phenotype were also reduced in tumors from AA patients ($p < 0.01$). Although no differences were observed in the overall NK cell populations, the prevalence of resting NK cells was greater in the AA tumors ($p < 0.01$) while the activated NK cell population was greater in EA tumors ($p < 0.01$). Taken together, the immunogenomics analysis suggested that AA patients have greater pro-tumorigenic immune characteristics compared to EA patients. Moreover, this analysis suggested that macrophages in EA tumors had a greater proportion with a M1 phenotype that is typically associated with a favorable immune response.

Table 2
Lymphocyte and macrophage subsets by race.

	All (N = 254)	European American (N = 196)	African American (N = 58)	p- value
B cells-naive	0.04	0.04	0.06	0.10
B cells- memory	0.02	0.01	0.03	< 0.001
Plasma cells	0.04	0.03	0.06	< 0.001
T cells-CD8	0.12	0.12	0.10	0.03
T cells-CD4 naive	0.00	0.00	0.01	0.15
T cells-CD4 memory resting	0.12	0.12	0.13	0.14
T cells-CD4 memory activated	0.01	0.02	0.01	0.18
T cells- follicular helper	0.07	0.06	0.07	0.20
T cells- regulatory	0.03	0.03	0.03	0.65
T cells-gamma delta	0.00	0.00	0.00	0.59
NK cells- resting	0.02	0.02	0.04	< 0.001
NK cells- activated	0.02	0.02	0.01	< 0.01
Monocytes	0.02	0.02	0.02	0.26
Macrophages- M0	0.14	0.14	0.11	0.13
Macrophages- M1	0.05	0.06	0.03	< 0.001
Macrophages- M2	0.20	0.20	0.19	0.49

Supplemental Table 1: Lymphocyte and macrophage fraction by race.

	All (N = 254)	European American (N = 196)	African American (N = 58)	p-value
	All (N = 254)	European American (N = 196)	African American (N = 58)	p-value
T cells CD8	0.12	0.12	0.10	0.03
T cells CD4	0.14	0.14	0.15	0.20
B cells	0.06	0.05	0.08	0.002
NK cells	0.04	0.04	0.05	0.28
Macrophage	0.39	0.40	0.34	0.003
Dendritic cells	0.01	0.01	0.01	0.67
Mast cells	0.08	0.07	0.08	0.36
Neutrophils	0.01	0.01	0.01	0.40
Eosinophils	0.00	0.00	0.00	0.69

Supplemental Table 2: Functional significance of distinct genes in AA vs. EA CRC

Gene	Functional significance	Clinical evidence
Downregulated		
IDO1	Impacts T-cell behavior via activity in tryptophan metabolism	Targeted therapies studied in melanoma and glioblastoma(30)
PDCD1 (aka PD1)	Expressed on pro-B-cells and plays role in cell differentiation	PD-1/PD-L1 pathway potential therapeutic target for CRC(31)
CD274 (aka PDL1)	T cell inhibitory receptor ligand	PD-1/PD-L1 pathway potential therapeutic target for CRC(31)
LAG3	Role in lymphocyte activation	Blockade studied in treatment of CRC liver metastases(32)
TNFSF9 (aka CD137L)	Cytokine associated with optimizing CD8 T-cell response	Differential levels in colon vs. rectal cancer with possible implications for carcinogenesis(33)

Supplemental Table 1: Lymphocyte and macrophage fraction by race.

	All (N = 254)	European American (N = 196)	African American (N = 58)	p-value
TNFRSF9 (aka CD137)	Associated with clonal expansion, survival and development of T cells.	Differential levels in colon vs. rectal cancer with possible implications for carcinogenesis(33)		
TNFRSF18 (aka GITR)	Plays role in self-tolerance mediated by CD25(+)CD4(+) regulatory T cells	Potential role in inhibiting Treg function concurrent with CD8 cell activation(34)		
Upregulated				
CD160 (aka NK1)	Binds MHC Class I. Expressed on intestinal lymphocytes associated with HVEM.	Associated with improved clinical outcome in hepatocellular carcinoma(35)		
TNFSF13B	Cytokine in TNF ligand family with role in proliferation and differentiation of B cells.	Associated with poor outcome in study of topoisomerase inhibitors in CRC(36)		
Supplemental Fig. 1: Correlation between MHC class 1 molecules and immune markers.				
Supplemental Fig. 2: Impact of MHC1 expression on progression-free survival.				
Supplemental Fig. 3: Impact of MHC1 expression on overall survival.				
Supplemental Table 1: Lymphocyte and macrophage fraction by race.				

Racial differences in CRC immune regulatory pathways

Considering the observed racial differences in the CRC tumor infiltrating immune cell populations, we also wanted to explore possible alterations in tumor immune regulatory pathways. Thus, we investigated the expression of previously reported immunostimulatory and immunoinhibitory gene profiles in both EA and AA patients (Fig. 3). In general, AA patients demonstrated a significantly decreased expression of immunoinhibitory genes compared with EA patients including IDO1 ($p < 0.01$), PD-1 (PDCD1) ($p = 0.01$), PD-L1 (CD274) ($p < 0.01$) and LAG3 ($p = 0.01$). Conversely, AA CRC tumors expressed relatively high levels of the immune regulatory molecule: CD160 ($p = 0.02$). In comparison, both racial groups expressed relatively high levels of other immune regulatory molecules such as CD28 and CD27. CRC tumors from AA patients manifested decreased expression of CD40, 4-1BB ligand (TNFSF9), 4-1BB (TNFRSF9), glucocorticoid-induced tumor necrosis factor receptor (TNFRSF18; GITR) and increased expression of B-cell activating factor (TNFSF13B) when compared to EA patients. Taken together, this immunogenomic analysis suggests higher expression of immune regulatory genes in AA versus EA CRC patients. Functional descriptions of differentially expressed genes are noted in Supplemental Table 2.

Racial differences in CRC MHC I and II expression

To further define potential drivers of the differences in immune regulation in AA versus EA CRC tumors, we investigated the relative expression of key mediators of antigen presentation including MHC class I, and II components (Fig. 4 and Supplemental Fig. 1). MHC class I molecules including HLA A, B, and C were decreased in AA CRC tumors and a similar pattern was observed for MHC class II molecules. Of the components for antigen presentation to the MHC class I pathway, TAP1 demonstrated the greatest reduction in expression (-9.6 fold) relative to EA CRCs. A correlation between MHC molecules and immune cell markers is presented in Supplemental Fig. 1. In addition, low expression of MHC molecules such as for TAP1 and TAP2 correlated with worse patient survival further supporting the clinical relevance of the racial differences in MHC expression (Supplemental Figs. 2 and 3).

Discussion

Investigating patient and tumor features that underlie well-established CRC racial disparities holds promise to uncover potential deficiencies in the tumor immune response of AA versus EA patients. Defining underlying cellular and molecular racial factors that promote poorer outcomes in AA patients may enable the design of therapeutic interventions to overcome disparities. Emerging studies suggest alterations in T cell presence and function in AAs may contribute to CRC disparities.(4, 26) Our group previously reported that low immune infiltrate in tumors from AA patients was more predictive of poor outcome.(4) To extend this line of investigation, we applied an immunogenomic analysis strategy to investigate CRC racial differences in gene expression data from TCGA.

Our evaluation of the tumor immune microenvironment revealed striking differences between AA and EA CRCs. AA CRC tumors displayed a decreased fraction of macrophages and CD8 T cells and an increased fraction of B cells compared with EA tumors in the tumor microenvironment, possibly suggesting a more favorable immune environment for anti-tumor immunity in EA cancers. The cellular outcomes persisted when controlling for sex, age and disease stage. Further differences were identified with respect to the expression of immunostimulatory and immunoinhibitory genes as well as MHC class I and class II molecules. Gene expression analysis demonstrated increased expression of immune regulatory molecules in EA patients including genes encoding for PD-L1 and PD-1. While expression of these molecules could reflect a more suppressive environment, these changes may independently reflect a general enhanced immune infiltration present in these tumors. Interestingly, a prior report found that African ancestry has also been associated with decreased PDL-1 expression across cancer types including colorectal adenocarcinoma, breast cancer, head and neck squamous cell cancer and papillary thyroid cancer.(21) In addition, the elevated macrophages, particularly M1 macrophages, is suggestive of a more favorable immune environment in EA CRCs.

The reduced expression of MHC class I and II in AA patient tumors was striking. While loss of MHC class I and II expression may reflect alterations in antigen processing in tumor or professional antigen presenting cells, it could also simply reflect a general reduced immune infiltration into the tumor,

especially in the possible reduction of IFN γ . Imaging studies defining MHC class I and II expression on different immune cells in the tumor will be necessary to address these possibilities. Given the critical role of tumoral antigen presentation in sustaining immune-based therapies (27–29), this finding is likely to be a key area of investigation for CRC racial disparities.

Seminal studies have established a strong relationship between increased peritumoral lymphocyte density and survival in CRC that exceeded the prognostic ability of TNM stage.¹¹ Wallace and colleagues from our institution supported the association between lymphocyte density and survival yet also identified a subset of young AA patients who fared poorly despite a high lymphocyte density suggesting that lymphocyte function and/or gene expression rather than density of cells may play a role in survival.⁶ In addition, previous work by Basa and colleagues demonstrated a significant decrease in granzyme B + infiltration for AA CRCs suggesting a decreased cytotoxic effect.¹⁷ Our current analysis builds on these observations suggesting that the antigen presentation process and T cell activity are globally reduced in AA patients resulting in less active cytotoxic T cells. The decreased expression of checkpoint mediators in AA tumors suggests that AA tumors compared with EA tumors have not activated specific T cell inhibitory pathways.

The results of this study must be evaluated in the context of its data source and study design. While TCGA is among the largest repositories of molecular cancer data available, the sample size specific to colorectal adenocarcinoma is small with the majority of tumor samples collected from EA patients. Though a wealth of molecular information is available through TCGA, certain information such as microsatellite stability are not readily available. Additionally, granular, patient-level socioeconomic and clinical data regarding patient treatment is unavailable in TCGA which allows for the possibility that differences in survival could be attributable to differences in access to care and treatment received. With respect to racial differences in progression free survival and tumor immune response, the mechanism by which racial differences in tumor immune response may underlie disparate clinical outcomes remains to be elucidated.

Abbreviations

Colorectal cancer (CRC); European Americans (EAs); African ancestry (AAs); The Cancer Genome Atlas (TCGA); tumor infiltrating lymphocyte (TIL); Major histocompatibility complex (MHC)

Conclusions

In summary, this secondary analysis of a large, publicly available CRC molecular data repository has identified significant differences in the tumor immune microenvironment of AA and EA tumor samples in the setting of a decreased disease specific survival for AA patients. While exploratory in nature, these differences call attention to varied immunological signatures for AA CRC as compared to EA CRC that may play a role in explaining not only the clinical differences in outcome between the groups but also provide possible targeted therapeutic opportunities.

Declarations

Ethics approval and consent to participate:

As these data are part of a de-identified, publicly available database, this does not constitute human subjects research and informed consent was not applicable. The Institutional Review Board of the Medical University of South Carolina approved this analysis.

Consent for publication:

Not applicable.

Availability of data and materials:

All data are publicly available as noted in the methods section.

Competing interests:

No conflicts to disclose.

Funding:

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Authors' Contributions:

Conception/design: Findlay, Rubinstein, Chung, Camp

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Figures

Figure 1

(A) Overall survival and (B) progression-free survival by race. The p-value in each subfigure indicates the log-rank test significance.

Figure 2

Immune cellular fraction estimates by race.

The heatmap presents averaged gene expressions (z-scores) for immuno-inhibitors and immuno-stimulators in each racial group. Log2 fold changes are provided, where * denotes *t*-test *p*-value < 0.05, indicating the significant racial differences in expressions between two racial group.

Figure 3

Association of immune modulating gene expressions with race. The heatmap presents averaged gene expressions (z-scores) for immuno-inhibitors and immuno-stimulators in each racial group. Log2 fold changes are provided, where * denotes t-test p-value < 0.05, indicating the significant racial differences in expressions between two racial group.

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Figure 4

Association of MHC gene expression with race. The heatmap presents averaged gene expressions (z-scores) for major histocompatibility complex (MHC) genes in each racial group. Log2 fold changes are provided, where * denotes p-value < 0.05, indicating the significant racial differences in expressions between two racial group.