High Intratumoral Hepatovirus Abundance in Colon Adenocarcinoma Is Associated with Worse Overall Survival and Increased Intratumoral CD8+ T Cell Infiltration

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INTRODUCTION

Emerging evidence suggests an important link between the intratumoral microbial and immune microenvironment in the pathogenesis of colon adenocarcinoma (COAD). Hepatovirus, a viral genus of the *Picornaviridae* family, is positively correlated with increased colon cancer risk but both its role in COAD tumorigenesis and association with patient survival remain unclear.

AIMS

To investigate whether intratumoral hepatovirus abundance in COAD is independently associated with overall survival and intratumoral immune cell response.

METHODS

We included patients with primary COAD and hepatovirus RNA sequencing (RNA-seq) data from The Cancer Genome Atlas (TCGA) COAD database. Intratumor hepatovirus abundance was estimated from data made publicly available by Poore et al.[1] Demographic and clinical data including age, sex, race, ethnicity, pathological tumor stage, and vitality were downloaded from TCGA-COAD database using cBioPortal.org. Intratumoral immune cell abundance data was downloaded from The Cancer Immunome Atlas (https://tcia.at/home) and estimated via quanTIseq, an RNA-seq deconvolution algorithm described previously by Finotello et al.[2]

Relative hazard ratios (HRs) for overall survival were estimated with Cox proportional hazards model using the lifelines python package. A significance threshold of $p \leq 0.05$ was used for independent t-tests. Spearman correlation analysis was then used to assess the association between intratumoral hepatovirus and immune cell abundance.

RESULTS

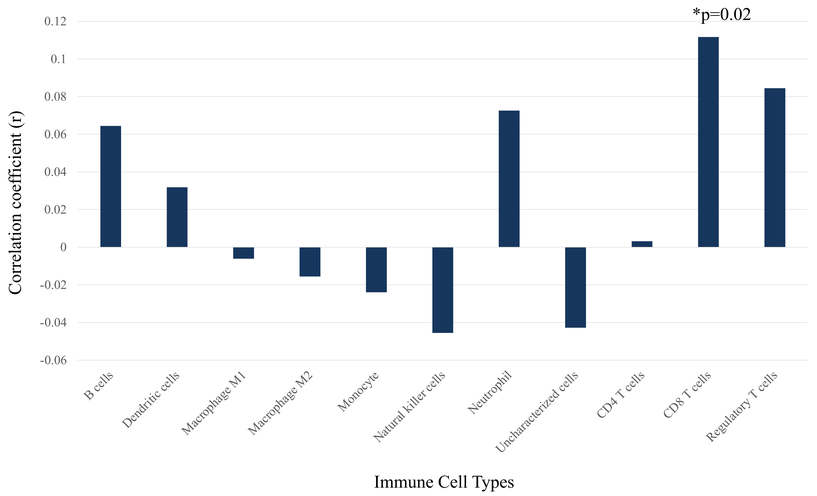
Table 1: Demographic and clinical characteristics of study participants

Parameter		N
Sex	Male	232
	Female	200
Age	>65	165
	≥65	267
Race	White	209
	African American	54
	Asian	10
	American Indian/ Alaskan Indian	1
	Unknown	158
Ethnicity	Non-Hispanic	260
	Hispanic	4
	Unknown	168
Pathological Tumor Stage	pT1	11
	pT2	74
	pT3	297
	pT4	50
Vitality	Living	235
	Deceased	95

Table 2: Association of intratumor hepatovirus abundance with overall survival using Cox proportional hazards model

Parameter		Hazard Ratio	P-value
Hepatovirus Abundance	Per unit increase in hepatovirus log2 transcripts per million	1.25	0.05
Age	Per year increase in age	1.02	0.03
Sex	Female	1	
	Male	1.02	0.93
Pathological Tumor Stage	pT1-pT2	1	
	pT3-pT4	1.02	0.03

Figure 1: Spearman correlation analysis of intratumor hepatovirus abundance and immune cell types



RESULTS

Our study included 432 participants with primary colon adenocarcinoma and hepatovirus RNA-seq data. The demographic and clinical characteristics of the study cohort are provided in Table 1. Intratumoral hepatovirus abundance was significantly associated with reduced overall survival (HR 1.25; p=0.05) in Cox proportional hazards model adjusted for age, sex, and pathological tumor stage (Table 2). As expected, older patients and those with advanced pathological tumor stage had higher mortality risk. Next, we sought to analyze associations between intratumoral hepatovirus abundance and immune cell response in COAD. Spearman correlation analysis showed intratumoral hepatovirus abundance was significantly positively correlated with intratumoral CD8+ T cell infiltration (correlation coefficient=0.11; p=0.02) but not with B cells, M1 macrophages, M2 macrophages, myeloid dendritic cells, monocytes, neutrophils, natural killer cells, CD4+ T cells, or regulatory T cells (Figure 1).

CONCLUSIONS

To our knowledge, this is the first study to identify an association between intratumoral hepatovirus abundance and overall survival in COAD. We also found a significant correlation between intratumoral hepatovirus and CD8+ T cell abundance, highlighting the potential role of hepatovirus in immune and inflammatory pathways regulating COAD carcinogenesis.

REFERENCES

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