Intratumoral Human Cytomegalovirus Abundance in Colon Adenocarcinoma Is Associated with Poor Survival Outcomes and Increased Intratumoral Regulatatory T-cell infiltrate in Elderly Patients

Saif Zaman, MD[1]; George Chen, MD[1]; Peter Block, MD[1]; Ankoor Patel, MD[2]; Daniel T Segarra, MD[3]; Petr Protiva, MD, MPH

[1]Yale School of Medicine, Department of Internal Medicine, Section of Digestive Diseases; [2]Robert Wood Johnson University Hospital, Department of Medicine; [3]University of South Florida, Department of Internal Medicine; [4]VA Connecticut Health Care System, Department of Medicine

INTRODUCTION

Although higher rates of human cytomegalovirus (CMV) are known to be associated with colorectal cancer, the impact of CMV on patient survival and its impact on the immune milieu in the tumor microenvironment have not been studied extensively. As such, we assess the associations of intratumoral CMV RNA signatures in colon adenocarcinoma, as derived from the work published by Poore et al. (Nature, 2020)[1] with overall survival and intratumoral immune cell abundance estimated via quanTIseq, an RNAseq deconvolution algorithm described previously by Finotello et al. (Genome Medicine, 2019)[2]

AIMS

To investigate how recovery of intratumoral CMV RNA sequences in Colon Adenocarcinoma (COAD) are associated with overall survival and intratumoral immune cell abundance

METHODS

Microbial RNA sequencing (RNA-seq) data was procured as described previously by Poore et al. and used to calculate average log counts per million (CPM) of CMV. Abundance of intratumoral immune cell types was estimated via the quanTIseq method described previously by Finotello et al. Cell abundance data was downloaded from The Cancer Immunome Atlas (https://tcia.at/home). The Cancer Genome Atlas Colon Adenocarcinoma clinical dataset was downloaded from cBioPortal.org. Only patients with primary tumor sites in the colon were included for further analysis. Survival data was processed using GraphPad Prism software to generate Kaplan-Meier curves. Relative hazard ratios (HRs) for overall and age-specific survival were estimated with cox proportional hazards models using the lifelines python package. The p-value level of significance was set at <0.05 for independent t-tests, with Bonferroni correction for multiple comparisons.

RESULTS

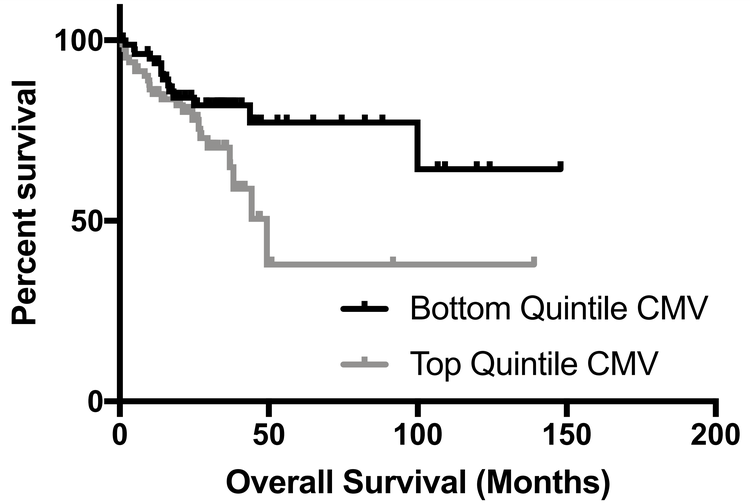

Figure 1. Overall Survival of COAD patients with top quintile of CMV recoveries compared to overall survival of COAD patients with bottom quintile of CMV recoveries

Table 1. Association of intratumor Cytomegalovirus abundance with overall survival risk in patients with colon cancer, using cox proportional hazards model

Model 1 (Age >= 65) (n = 267)		
	HR	p-value
Cytomegalovirus	1.21	0.000908
Age	1.04	0.0243
Sex (male/female)	1.04	0.941
Disease stage (I-II/III-IV)	3.871	0.008864
Model 2 (Age < 65) (n = 165)		
	HR	p-value
Cytomegalovirus	0.943	0.769
Age	0.949	0.234
Sex (male/female)	0.940	0.910
Disease stage (I-II/III-IV)	3.44	0.233

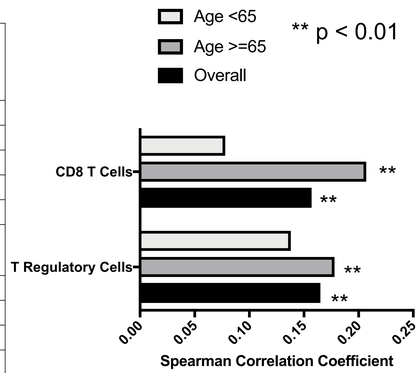

Figure 2. Spearman Correlation Coefficient between CMV recoveries and CD8+ T cell and T regulatory cell recoveries

RESULTS

Our study included 432 patients with primary colon adenocarcinoma and CMV RNA-seq data. Comparison of the rate of overall survival for patients in the top and bottom quintiles of CMV recoveries showed higher CMV abundance was associated with significantly decreased survival (p=0.04) (**Figure 1**). When stratified by age, individuals aged ≥65 with higher CMV abundance had increased overall mortality risk (HR 1.21; p<0.001) while no significant association was observed between CMV abundance and survival in those aged ≤65 (**Table 1**). Spearman correlation analysis showed intratumoral CMV signatures were significantly positively correlated with CD8+ T cell (correlation coefficient=0.20; p=0.001) and regulatory T cell (correlation coefficient=0.17; p=0.005) abundance in individuals aged ≥65 but not in those aged ≤55 (**Figure 2**).

CONCLUSIONS

Our results demonstrate that there is an association between CMV RNAseq signatures in tumor tissue and worse overall survival outcomes of patients with colon adenocarcinoma. Our results suggest this overall survival association may additionally be associated with age. Additionally, our results demonstrate that the recovery of CMV RNAseq signatures correlate with intratumoral immune cell infiltrates when assaying with the quanTIseq algorithm. To our knowledge, this is the largest study investigating associations of intratumoral CMV signatures with patient survival in colon adenocarcinoma and the first to characterize an age-specific correlation between intratumoral CMV and immune cell abundance. Further research elucidating the molecular mechanisms by which CMV modulates the tumor immune response is warranted.

Contact Information – Please note that the lead author is currently presenting other posters, if there are any questions please contact at 203-909-7097

REFERENCES

1. Poore, G.D., et al., Microbiome analyses of blood and tissues suggest cancer diagnostic approach. Nature, 2020. 579(7800): p. 567-574.
2. Finotello F, Mayer C, Plattner C, et al. Molecular and pharmacological modulators of the tumor immune contexture revealed by deconvolution of RNA-seq data. Genome Med. 2019;11(1):34.