Increased Primary Tumor Sutterella Bacterial RNAseq Signatures are Associated with Increased M2 Macrophage Abundance and Worse Overall Survival in Rectal Adenocarcinoma

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[1,4]

[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 gut microbiome dysbiosis has been implicated in colorectal cancer, the role of intratumor microbiome in carcinogenesis has not been studied extensively. We aimed to identify intratumor bacterial genera, as derived from the work published by Poore et al. (Nature, 2020)[1], that are significantly correlated with M2 macrophage abundance in rectal adenocarcinoma and analyze associations of those bacterial genera with overall survival.

AIMS

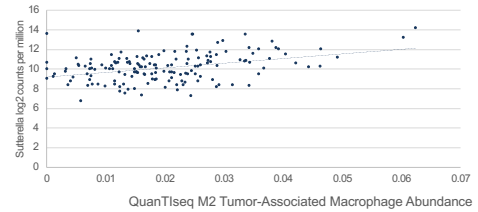
To investigate how recovery of intratumoral bacterial RNA sequences in Rectal Adenocarcinoma (READ) are associated with overall survival and intratumoral immune cell abundance

METHODS

RNA sequencing (RNA-seq) data for 1206 bacterial genera with all putative contaminants removed was procured from data made publicly available by Poore et al. Intratumor M2 TAM abundance was first estimated by quanTIseq[2], an RNAseq deconvolution algorithm, and verified by CIBERSORT[3], another RNAseq-based in silico approach for characterizing cell subsets in tumor samples. Cell abundance data was downloaded from The Cancer Immunome Atlas (https://tcia.at/home). Pearson correlation analysis of intratumor abundance of each bacterial genus and M2 TAM was conducted. Bonferoni correction was used for multiple comparisons correction. Next, for bacterial genera correlated with M2 TAM abundance, we analyzed their associations with overall survival in rectal adenocarcinoma using clinical data from The Cancer Genome Atlas Rectal Adenocarcinoma database, downloaded from cBioPortal.org. Only patients with primary tumor sites in the rectum (n=158) were included for analysis. Relative hazard ratios (HRs) for overall survival were estimated with cox proportional hazards models using the lifelines python package, with p-value threshold set at <0.05 for independent t-tests.

RESULTS

A



B

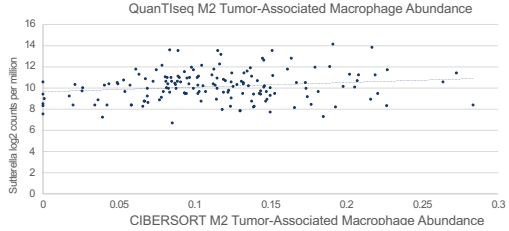


Figure 1. Pearson Correlation analysis of Sutterella recoveries with M2 macrophage abundance using quanTIseq and CIBERSORT methods.

Table 1. Associations of intratumor Sutterella abundance, sex, and tumor stage with overall survival in patients with rectal adenocarcinoma using Cox proportional hazards models (n = 151)

Parameter		Hazard Ratio (HR)	ln (HR)	95% Confidence Interval ln (HR)	P-value
Sutterella abundance	Per unit increase in Sutterella log2 counts per million	1.45	0.37	0.071 – 0.673	0.015
Age	Per year increase in age	1.11	0.10	0.047 – 0.153	0.0002
Sex	Female	1			
	Male	1.09	0.083	-0.722 – 0.889	0.84
Pathologic Tumor stage	pT1-pT2	1			
	pT3-pT4	0.80	-0.223	-1.361 – 0.915	0.701

RESULTS

Among 1206 bacterial genera with RNA-seq data, Sutterella was the only bacterial genus significantly positively correlated with M2 TAM abundance estimated via the quantiSeq method after Bonferroni correction (Pearson correlation coefficient=0.38; p=6.7E-7) (**Figure 1A**). This significant correlation was replicated in correlation analysis using M2 TAM abundance estimated via the CIBERSORT method (Pearson correlation coefficient=0.17; p=0.03) (**Figure 1B**). In 151 patients with primary rectal adenocarcinoma, intratumor Sutterella abundance was significantly associated with worse overall survival (HR 1.45; p=0.02) after adjusting for age, sex, and tumor stage (**Table 1**). It is possible that stage is not associated with overall survival in this cohort due to the distribution of tumors at various pathological stages.

CONCLUSIONS

To our knowledge, this is the first study to identify associations of intratumor Sutterella , a genus of bacteria that has previously been isolated from human feces[4], with abundance with M2 macrophages in rectal adenocarcinoma. Perhaps Sutterella abundance in the tumor is associated with increased inflammation, and as a result is associated with the results we demonstrate here, highlighting the need for further investigation of mechanistic pathways linking intratumor microbiome and carcinogenesis.

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

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