The Impact of the Tumor Microbiome on Anti-tumor Immunity in Mucosal Melanoma

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Introduction

Mucosal melanoma is a rare, but lethal, form of melanoma.

% of US Cases: 87% 3% 1% 5%

5-year survival rate: 81% 75% 60%

Figure 1. Cutaneous melanomas and different rare, non-sun related melanoma subtypes. Mucosal melanomas are typically not detected until late stage, are challenging to surgically resect, and respond poorly to standard melanoma treatments including immune checkpoint blockade (ICB) therapy.

Mucosal melanoma responds poorly to immune checkpoint blockade (ICB) compared to cutaneous melanoma.

Hypothesis

Given the role of the microbiome in tumor immunity and ICB response, we hypothesize distinct mucosal tissue microbiomes contribute to poor anti-tumor immunity and ICB resistance in mucosal melanoma.

Methods

Patient gDNA specimens 16S rRNA bacterial sequencing

Patient Tumors Patient Bloods 16S rRNA genes Bacterial diversity and sample 16S rRNA sequencing process

Figure 5. 16S rRNA sequencing of melanoma patient specimens. (A) Specimens were collected by the CU Melanoma Biorepository under CDMRP 405-0305. Genomic DNA was purified using the Qagen Ohexy UltraClean Bacterial Kit (tumors) or Dnaeasy PowerSoil Pro Kit (blood). (B) Diagram of 16S rRNA sequencing process.

Results

~50% of tumors are "positive" for bacteria

Primary mucosal melanoma tumors have higher bacterial load vs cutaneous melanomas

Mucosal melanoma tumors have more bacteria species vs cutaneous melanomas

Tumors clustering with stools are mucosal melanoma tumors

Results (Cont.)

Mucosal melanoma tumors have proportions of bacteria consistent with poor anti-tumor immunity

Figure 9. Impacts on Immune Genes in Vitro. (A) TLR 10 Interferon Pathway end point products show a variable response. (B) Inflammatory cytokines resulting from LPS pathway, markedly decreased IL-6 expression.

Conclusions

- Mucosal melanoma is a rare, but particularly lethal, form of melanoma which responds poorly to ICB compared to cutaneous melanomas.
- The mucosal melanoma tumor microbiome is significantly different from cutaneous melanoma, and it more closely resembles the gut microbiome.
- MM tumors have unfavorable proportions of bacteria species controlling tumorigenicity and immunity.

Future Directions

- Multiomics analysis with RNAseq and ATACseq to determine the correlation between the microbiome and epigenetic-mediated immune gene silencing in mucosal melanoma.
- Mucosal melanoma microbiome (gut and tumor) reconstitution in mice to determine effect on tumor epigenetics, immune, and ICB response.
- ITS sequencing of specimens for fungal species analysis.

References


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