Comparative Analysis Between the Tumor Immune Microenvironments of Microsatellite-Stable and Microsatellite Instability-High Colorectal Primary and Metastatic Sites

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INTRODUCTION

In colorectal cancers, characteristics of the tumor immune microenvironment (TIME) carry valuable implications for treatment resistance and/or response to immunotherapies. We have previously reported significant differences between the TIMEs of primary colorectal cancer (CRC-P) and CRC samples from various metastatic sites. Increased immune cell infiltration, B-cells, and CD8 cells, and decreased macrophages were noted in CRC-P and lung metastatic (LuM) lesions compared to liver (LM) and peritoneum (PM) metastases.

Here, we expanded our work to microsatellite instability-high (MSI-H) CRC and compared their TIME to respective microsatellite-stable (MSS) tumor sites.

METHODS

- De-identified cases of MSS (n=6,732) and MSI-H (n=208) metastatic CRC that underwent next-generation sequencing with the Tempus xT assay were selected from the Tempus Database.
- Gene expression patterns of immune cells, including B, T (CD4+, CD8+), NK cells, and macrophages, were used to predict relative intra-tumor abundance.
- MSI-H and MSS cohorts included CRC-P, LM, and PM. LuM was analyzed only in MSS tumors due to the limited number of MSI-H LuM. There was not a sufficient number of MSI-H Lung metastasis (n=5) to include in the analysis.
- Tumor mutational burden (TMB), neoantigen burden, and proportion of immune cells in CRC-P, LM, and PM were compared across MSI-H and MSS patients.
- Chi-squared/Fischer's exact tests or Kruskal-Wallis tests were used to assess statistical significance.

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SUMMARY

- MSI LM and PM have a more favorable TIME than respective MSS metastases, explaining the discordance in response to checkpoint inhibitors (CPI) and reported CPI benefits in MSI cases across all metastatic sites.
- MSS LuM have a comparable TIME to MSI metastatic sites, explaining the recently reported benefits from CPI therapy in this group.

RESULTS

Figure 1. TMB and Neoantigen Burden Across Primary and Metastatic Sites of MSI-H Patients

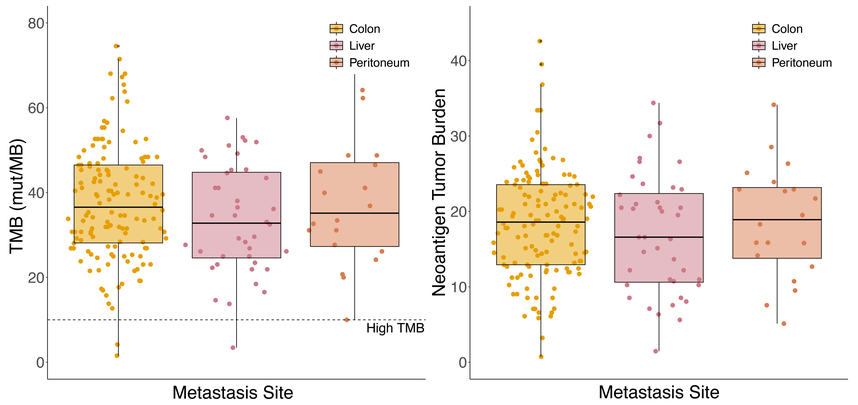

Figure 1. There was no difference in TMB or neoantigen burden across primary and metastatic sites of MSI-H patients (p=0.2 and p=0.4, respectively).

Figure 2. TMB and Neoantigen Burden between MSI-H and MSS Primary and Metastatic sites

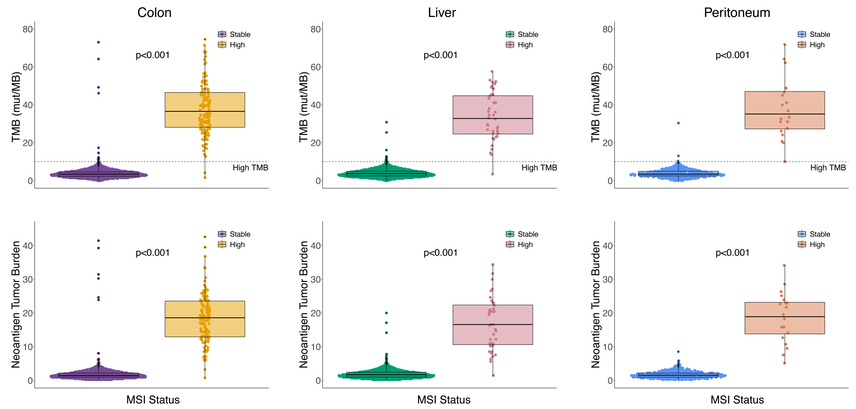

Figure 2. The median TMB and neoantigen tumor burden was significantly higher in the MSI-H cohort compared to the MSS cohort, irrespective of primary and metastatic sites

Figure 3. TIME Comparison Between MSS and MSI-H Primary and Metastatic Sites

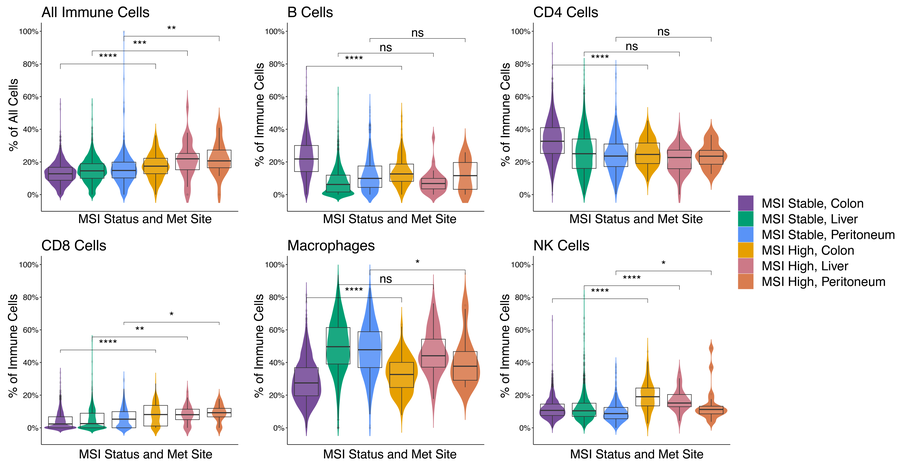

Figure 3. Compared to MSS cases, the MSI-H cohort had a higher percentage of immune cells relative to all cell types, irrespective of tumor site. Within the immune infiltrate only, CD8 and NK cell percentages were higher in MSI-H cases across all tumor sites, and CD4 cell, B cell, and macrophage percentages were higher in MSI-H cases among colon metastases. In the immune infiltrate, macrophage proportions were also higher in MSI-H cases among peritoneum metastases (*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001).

Figure 4. Comparison of MSS Lung metastases TIME with MSI-H Liver and Peritoneal Metastases

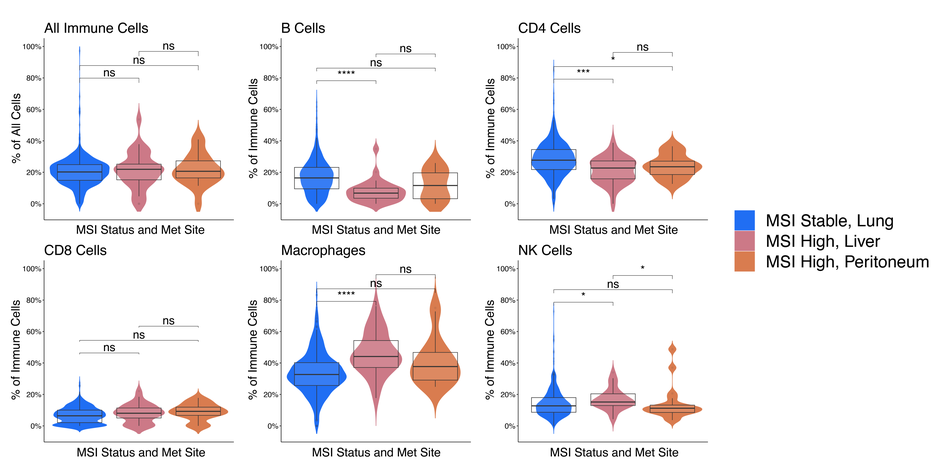

Figure 4. Compared to MSI-H liver and peritoneum cases, MSS lung metastases had a similar percentage of immune cells relative to all cell types and CD8 cells relative to all immune cells. Within the immune infiltrate only, MSS lung metastases had a higher percentage of B and CD4 cells, and a lower percentage of macrophages and NK cells compared to the MSI-H liver sites (*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001).