Genomic and immune infiltration differences between MSI and MSS GI tumors.

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ABSTRACT

Background: DNA mismatch repair pathway dysfunction is a major hallmark of MSI tumors, which are associated with genetic instability and are linked to numerous genetic syndromes such as Lynch syndrome. MSI is determined via a combination of DNA sequencing and immunohistochemistry, and is found in 5-10% of GI tumors. MSI is associated with tumor microenvironment (TME) alterations and is linked with better outcomes in colorectal cancer (CRC).

Methods: We performed whole genome sequencing (WGS) on a total of 52 GI tissue samples. We performed target enrichment using a panel designed by Guardant Health. We performed bulk sequencing, single-cell, and spatial transcriptomics and immunochemistry. We performed bulk sequencing, single-cell, and spatial transcriptomics and immunochemistry.

Results: We identified significant differences in TME infiltration between MSI and MSS tumors, with MSI tumors having higher immune cell infiltration and MSI tumors having lower immune cell infiltration

Conclusions: We conclude that MSI tumors have a unique TME, with higher immune cell infiltration and lower immune cell infiltration compared to MSS tumors. This finding has implications for the development of targeted therapies for MSI tumors.

RESULTS

MSI high and low samples in transcripational space

MSI vs. MSS tumor expression in colorectal tumors

Expression levels of immune markers in MSI high and low groups

KEY FINDINGS

- Higher immune signaling in MSI high tumors
- Metabolic signaling is up in MSS group
- Upregulation of structural cellular integrity pathways in MSI high samples
- Some MSI samples show high CD8 T cells enrichment
- TIM3 and LAG3are expressed at higher levels in MSI high samples

CONCLUSIONS:

MSI tumors demonstrate higher immune signaling, with many immune and checkpoint markers expressed at higher levels in MSI tumors. Some cellular integrity pathways also appear to be up in MSI cohort. A number of potentially important somatic variants are associated with MSI samples.