OVERCOMING IMMUNE RESISTANCE IN MMRD TUMORS

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Background Patients with Lynch Syndrome, an inherited mismatch repair deficiency, have an increased risk for developing microsatellite unstable (MSI-H) cancers. Our team recently identified shared immunogenic frameshift peptides in patient tumors that can be targets of T cell surveillance and preventative MSI-H cancer vaccines. We hypothesize that in Lynch Syndrome some premalignant lesions are capable of evading immune surveillance from cytotoxic T lymphocytes due to immune checkpoint expression and immunosuppression from tumor, myeloid and stromal cell populations. Immune checkpoint blockade (ICB) showed promising results in the treatment of MSI-H tumors and are being evaluated in the adjuvant setting of patients with Lynch syndrome post surgical resection. However, a significant percentage of advanced MSI-H tumors resist ICB suggesting evolving mechanisms of immune resistance.

Methods We will use a MSI-H in vivo mouse model and additionally develop 3D spheroids cocultured with immune cells to characterize the underlying immune resistance mechanisms. We will quantify MSI-H tumor growth and immune infiltration in the MSI-H mouse model, with or without ICB. We will analyze the presence of immunosuppressive pathways and myeloid subsets in high growth resisting tumors by immunohistochemistry, scRNAseq, spatial transcriptomics and flow cytometry. In addition, we will perform short-term in vitro spheroid-splenic cell co-cultures to better characterize the early immune resistance mechanisms.

Results Our results show that targeting multiple checkpoints and myeloid compartments limit immune resistance following anti-PD-1.

Conclusions Targeting multiple checkpoints and myeloid immunosuppressive programs may be beneficial to target MMRd tumors.

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