Tumor Ablation By Irreversible Electroporation Augments PD-1 Checkpoint Inhibitor Immunotherapy In Colon Adenocarcinoma:

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Abstract:
Introduction: Programmed Cell Death Protein 1 (PD-1) checkpoint inhibitors have recently been approved for microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC). Response rates are promising in MSI-H-dMMR CRC but remain dismal for microsatellite-stable (MSS) or mismatch repair proficient (pMMR) CRC. >80 percent of CRCs are MSS-pMMR. Increasing tumor infiltrating lymphocytes (TILs) may improve checkpoint inhibitor efficacy in CRC. New data suggest irreversible electroporation (IRE) therapy whereby electric pulses cause tumor necrosis and apoptosis; increases tumor associated protein uptake by dendritic cells, subsequently boosting neoantigen presentation and TILs. We hypothesized IRE combined with anti-PD-1 antibody, when compared to IRE or anti-PD-1 antibody alone, would increase survival, cause tumor regression by increasing TILs, and guard against secondary tumor challenge by increasing tumor antigen specific CD8 T cells.
Methods: Using the MC38 cell line derived from murine colon adenocarcinoma, immunohistochemistry, and anti-CD8 antibodies we evaluated anti-tumor immune responses in mice.
Results: IRE with anti-PD-1 antibody showed statistically significant survival, tumor regression, and increased TILs compared to IRE or anti-PD-1 antibody alone. 17/18 mice treated with IRE and anti-PD-1 antibody rejected a secondary tumor challenge. Conversely, IRE with anti-PD-1 antibody failed to protect against tumor rechallenge in mice that underwent CD8 T cell depletion. 0/10 CD8 T cell depleted mice survived after secondary tumor challenge.
Conclusion: These data suggest IRE and anti-PD-1 antibody work in concert to bolster tumor specific CD8 T cell immune responses, serving as a pragmatic strategy for overcoming clinical challenges in checkpoint inhibitor immunotherapy for CRC.