RHABDOID TUMORS ARE IMMUNOGENIC AND MAY RESPOND TO IMMUNOTHERAPY

Low tumor mutational burden (TMB) is associated with low expression levels of tumor-associated antigens; in principle, this should result in a reduced response to immune-checkpoint blockade (ICB). However, Leruste and colleagues found that this may not apply to rhabdoid tumors, a group of pediatric soft-tissue cancers with very low TMB. An analysis of 114 samples from both extracranial (ECRT) and intracranial (AT/RT) primary rhabdoid tumors revealed greater immune-cell infiltration in the ECRT, MYC-AT/RT, and TYR-AT/RT subgroups than in the SHH-AT/RT subgroup. Further, the extent of immune-related cytolytic activity among the non-SHH rhabdoid tumors matched that of some of the most immunogenic known tumor types (e.g., adult lung adenocarcinoma and melanoma). The rhabdoid tumors were infiltrated by large numbers of both T-cell and myeloid-cell populations, and the phenotypes of these immune cells implied an active and ongoing anti-tumor response. The tumor immune infiltrates of the ECRT and MYC-AT/RT subgroups exhibited marked clonal expansions of tumor-resident and exhausted memory CD8+ T cells, probably resulting from a tumor-specific response by the adaptive immune system. Notably, tumor-infiltrating CD8+ T cells had high expression of clinically targetable inhibitory immune-checkpoint receptors, including PD-1, TIM3, and LAG3. This observation prompted experiments probing whether rhabdoid tumors were susceptible to ICB. In a mouse MYC-AT/RT model, PD-1 blockade prolonged survival and caused complete tumor regression in 67% to 80% of treated mice. Upon rechallenge using syngeneic grafts of the same tumor type, all cured mice rejected the new tumors, indicating that the treatment had resulted in immunity. Mechanistically, re-expression of endogenous retroviruses resulting from deficiency of the SWI–SNF complex component SMARCB1—some mutations in which are known to drive rhabdoid-tumor development—appeared to contribute to activation of the immune response in rhabdoid tumors. Together, these results suggest that immunotherapy may be more effective than would have been predicted for rhabdoid tumors and add to a growing body of evidence that the immunogenicity of tumors is not solely dictated by TMB.


BONE-METASTASIS MICROENVIRONMENT MAY EXPLAIN IMMUNOTHERAPY RESISTANCE

The use of immune-checkpoint blockade (ICB) is effective in some patients with metastatic castration-resistant prostate cancer (CRPC), but efficacy in patients with bone metastases is limited. In paired pre- and post-treatment primary prostate tumors and bone marrow samples from the same patients, Jiao and colleagues found that anti-CTLA4 (specifically, ipilimumab) treatment caused T1,1 expansion in the prostate tumors, but not in the bone marrow, which instead exhibited an increase in cells of the T1,17 lineage. Treatment with anti-CTLA4 and anti–PD-1 caused tumor regression and improved overall survival in mice injected subcutaneously with prostate-cancer cells but had little effect on prostate-cancer cells injected into the bones despite triggering an expansion of tumor-infiltrating T cells in both models. In the bone CRPC model, the CD4+ T-cell population was composed solely of regulatory T cells (Treg) and T1,17 cells, and the population of the latter increased after ICB treatment. Notably, T1,1 effector cells were lacking in the bone CRPC tumors, which may explain the inferior response of these tumors to ICB. Compared with bone marrow from tumor-free femurs, bone marrow from tumor-bearing femurs had increased TGFβ1 levels, which may have resulted from an observed increase in osteoclast-mediated bone resorption. In the mouse bone CRPC model, combination treatment with anti-CTLA4 and anti–TGFβ reduced tumor growth and improved overall survival more than either treatment alone, and the combination treatment resulted in an increase in T1,1 cells and a decrease in Tregs in the tumor-infiltrating T-cell population. Further experiments revealed that the combination treatment caused a clonal expansion of tumor-specific CD8+ T cells, most of which exhibited a memory–effector signature. Together, these findings suggest that TGFβ-mediated restriction of development of the T1,1 lineage along with insufficient expansion and activation of CD8+ T cells may be responsible for the resistance of CRPC bone metastases to ICB. Additionally, this study demonstrates that combination therapy with ICB and anti-TGFβ may be worth investigating.

Rhabdoid Tumors Are Immunogenic and May Respond to Immunotherapy


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