

Depletion of tumor-infiltrating neutrophils invigorate antitumor immunity in PD-1 blockade-resistant urothelial cancer

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Abstract

Bladder cancer, a significant health issue in the U.S., is the fourth most common cancer in men and ninth in women, with approximately 67,000 new cases and 13,750 deaths annually. Despite early diagnosis, many cases advance, necessitating improved treatments through research and clinical trials. Recent immunotherapy advances have boosted survival in solid tumors, including urothelial cancer. However, PD-1 blockade is effective in only about 30% of metastatic urothelial cancer (mUC) patients, with poor prognostic indicators for pembrolizumab including high ECOG-PS, liver or visceral metastases, high neutrophil-lymphocyte ratio (NLR), elevated c-reactive protein (CRP), and low Geriatric Nutritional Risk Index (GNRI). A decrease in NLR post-chemotherapy is linked to better survival with Pembrolizumab, suggesting NLR changes affect the immune environment. Tumor-associated neutrophils (TANs) and myeloid-derived suppressor cells (MDSCs) contribute to resistance by modulating the tumor microenvironment. Specific subsets of neutrophils, such as PMN-MDSCs, are associated with PD-1 blockade resistance. This study aimed to explore the impact of TANs on mUC survival and the potential of PMN-MDSC inhibition combined with PD-1 blockade. Findings showed that specific intratumoral neutrophil subsets influence survival, PMN-MDSCs are enriched in resistant models, and their depletion boosts antitumor activity by increasing CD8⁺ lymphocytes.