

MECHANISMS OF IMMUNE ESCAPE IN NF1-ASSOCIATED PERIPHERAL NERVE SHEATH TUMORS

¹Lindy Zhang*, ^{1,2,3}Alexandre Maalouf, ¹Ana Calizo, ^{1,2,3}Aditya Suru, ^{1,3}Stavriani Makri, ⁴Jineta Banerjee, ^{1,3}John Gross, ^{1,3}Christine Pratilas, ^{1,2,3}Nicolas Llosa. ¹*Johns Hopkins University School of Medicine, Baltimore, MD, USA*; ²*Bloomberg-Kimmel Institute for Cancer Immunotherapy, Baltimore, MD, USA*; ³*Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA*; ⁴*Sage Bionetworks, Seattle, WA, USA*

Background Neurofibromatosis type 1 (NF1) is a neurogenetic condition with stereotypic cutaneous findings and a predisposition for benign and malignant tumors. About half of patients will develop plexiform neurofibromas (PN), non-malignant tumors that have a 10% lifetime risk of developing into aggressive soft tissue sarcomas called malignant peripheral nerve sheath tumors (MPNST). Some lesions, denoted atypical neurofibromatous neoplasms of uncertain biologic potential (ANNUBP), exhibit histopathologic features and are precursors to MPNST. Despite many clinical trials, there has been little advancement in treatment outcomes and overall survival remains poor; therefore, new therapeutic approaches are needed. PNST are composed of transformed Schwann cell precursors that interact with infiltrating immune cells. An understanding of the relationship between the pre-existing immunity and tumor microenvironment (TME) will help unveil potential for immunotherapeutics.

Methods We used complementary techniques to interrogate the TME in NF1-associated PNST. 15 pNF, 8 ANNUBP, and 18 MPNST specimens were analyzed to compare the quantitative and spatial resolution of the geography and nature of tumor infiltrating immune cells during progression to malignancy. We determined the interactions of immune cells and immunoregulatory molecules, using a combination of multiplex flow cytometry (MFC) and gene expression profiling studies. Lastly, we correlated these findings with clinical outcomes.

Results Immunophenotyping confirmed the higher presence of infiltrating myeloid compared to lymphoid cells, with a predominance of CD163+ myeloid cells during malignant transformation. Similarly, transcriptomic data showed significant accumulation of immunosuppressive myeloid populations in MPNST. The MPNST TME was consistent with an immune excluded phenotype on spatial resolution. MFC further characterized CD163+ myeloid cells as immunosuppressive with a high PD-L1 expression. Higher expression of CD8+ T cells and lower PD-L1 in MPNST correlated with improved survival.

Conclusions An immunosuppressive microenvironment characterizes PNST during the process to malignancy, generating an immune-excluded phenotype. This progression of pre-malignant tumors to malignancies can respond to the principles of immunoediting; thus, we believe that immunotherapies may be a therapeutic option in patients with MPST. Further studies on PD-L1 expression may reveal it as a useful biomarker. The mechanisms of immune modulation in PNST will inform interventions to stimulate anti-tumor immunity in this disease.

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