Immunosuppressive microenvironment in neuroendocrine neoplasms

Abstract

Introduction: Immunotherapy with checkpoint inhibitors has shown promising results in a variety of tumors. But in neuroendocrine tumors (NET) and neuroendocrine carcinomas (NEC), low response rates to anti-PD1 monotherapies have been reported.

Objective: We aimed herein to investigate the tumor immunomicroenvironment to determine whether checkpoint pathways like PD-1/PD-L1 might play a role in immune escape and whether other immune escape mechanisms might need to be targeted to enable a functional active anti-tumor T cell response in NET/NEC.

Methods: 48 NET and 30 NEC samples were analyzed by immunohistochemistry (IHC) and mRNA immunoprofiling including digital spatial mRNA profiling (DSP) using NanoString Geomax.

Results: Through IHC, both, NET/ NEC showed stromal CD3+ T cell infiltration, but less intratumoral T cell infiltration, although significantly higher in NEC compared to NET. Expression of checkpoint molecules like PD1, PD-L1 and TIM3 on immune cells was low or nearly absent.

mRNA immunoprofiling including DSP revealed low expression of IFNγ inducible genes neither in NET nor in NEC without any spatial heterogeneity. However, we observed an increased mRNA expression of chemokines, that attract myeloid cells, but not T cells, in NET and NEC, and high abundance of genes related to immunosuppressive myeloid cells and genes with immunosuppressive functions like *CD47*and *CD74*.

Conclusion: NET and NEC lack signs of an activation of the adaptive immune system, but rather show abundance of several immunosuppressive genes that represent potential targets for immunomodulation such as the innate immune checkpoints CD47 and CD74.