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Enriched Immune Cell Activities in the Tumor Microenviroments of Metastatic Pancreatic Neuroendocrine Tumors

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BACKGROUND: Despite a five-fold increase in the incidence of neuroendocrine tumors (NETs) over the last thirty years, molecular and immunologic basis for the development of NET metastases is not well characterized. Here we investigated the immune microenviroment of PNETs through use of RNA-sequencing and immunocytochemistry (IHC) and examine how it may contribute to the metastatic phenotype.

METHODS: We performed RNA-sequencing analysis on 11 metastatic and 15 localized PNETs from separate patients and utilized this data to perform molecular pathway analyses. DAVID pathway analysis was performed for 533 differentially expressed genes. IHC for specific immune-related genes was performed on paraffin-embedded blocks of both localized and metastatic PNETs.

RESULTS: David pathway analysis showed immune response genes and T-cell activation genes as the most enriched gene ontology terms, indicating strong immune regulation in metastatic PNETs. Metastatic tumors were associated with significant increase in expression of cytotoxic T-cell markers CD3 and CD8, which was validated using IHC staining ($p<0.01$). Additionally, RNA levels of cytolytic genes such as granzyme A and perforin 1 in metastatic PNETs were significantly increased relative to localized tumors ($p<0.01$). Interestingly, metastatic PNETs

had significantly elevated expression levels of T-cell exhaustion and suppression genes PD-L2, LAG3, TIM3, and galectin 9 ($p<0.01$). By applying CIBERSORT, a computational method to detect immune cell subsets, we found metastatic PNETs had significant enrichment of M2 macrophages, which are associated with immune suppression and tumor progression.

CONCLUSION: Metastatic PNETs appear to have a significant T-cell infiltrated phenotype with an associated increase in expression levels of T-cell exhaustion genes and immune suppressive milieu when compared to localized tumors perhaps portending blunted immune response. Comprehensive characterization of immune cell phenotypes and function in PNETs would be critical to further understand the interactions between the immune system and tumor growth allowing for future studies exploiting these mechanisms for potential therapeutic benefits.