Spatial Tumor-Immune Protein Signatures and Targets Associated with Prognosis and Subtypes of Ovarian Carcinoma

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Background: Immune checkpoint blockade has shown modest effect in ovarian carcinoma (OC), despite demonstrated effect of immune infiltration on prognosis and therapy resistance. The low success rate is likely due to the vast heterogeneity of pheno- and genotypic subtypes, combined with a highly variable immune response. There is an urgent need for comprehensive tumor-immune profiling to guide treatment selection. Here, we used Digital Spatial Profiling to 1) characterize regions of distinct tumor-immune microenvironment phenotypes and 2) identify signatures associated to OC subtypes and prognosis.

Methods: Two retrospective OC cohorts (Gothenburg Regional Ethics Review Board reference 201–15) were analyzed using GeoMx Digital Spatial Profiling. In the first cohort, 49 immune proteins were profiled in 50 OC. PanCK (tumor) and CD45 (immune) segments were separately profiled in 102 regions of diffuse, focal or insignificant immune infiltration. The second, larger OC cohort served to identify signatures related to OC subtypes and prognosis through profiling of 78 proteins in tumor cell (n=654) and stroma cell (n=259) regions. Biomarker signatures were identified using linear mixed effect and cox mixed effect models. Image analysis included cell segmentation, classification and network graph analysis.

Results: The spatial distribution of immune cells was prognostic, while overall level of immune infiltration was not. Areas of diffuse immune infiltration displayed more immune suppressive targets, while focal immune infiltration had higher levels of CD163 macrophages and granulocytes. Tregs and fibroblasts were associated with immune exclusion. High- and low-grade serous (HGSC, LGSC) and endometrioid OC displayed diverse immune infiltration patterns, while mucinous and clear cell OC had either focal or insignificant immune infiltration. HGSC had more T-cells, NK-cells, and CD68+ macrophages, while low-grade carcinomas displayed immune profiles of hematopoietic progenitor cells and granulocytes. HGSC, LGSC, mucinous and clear cell OC showed unique immune profiles and tumor and immune targets. STING was identified as a prognostic target across OC subtypes.

Conclusions: Profiles of targetable tumor- and immune markers differ significantly between OC subtypes and also vary according to immune infiltration pattern. The number of interactions between tumor and immune cells is more prognostic than the overall level of immune infiltration. Tumors with high stromal/local immune content may be more efficiently treated with immune modulation targeting immune suppressive innate markers, while PD-L1, IDO1 or Tim-3 mono- or combinatorial inhibition is likely more effective in tumors with diffuse infiltration. Together, these observations demonstrate the potential for spatially resolved profiling of tumor-immune microenvironments for precision medicine.

Ethics Approval: Collection, archiving and molecular analysis of the tissue material used in this retrospective study was approved by Gothenburg Regional Ethics Review Board, Sweden, reference 201–15.

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