1102 THE HLA-E/NKG2A AXIS IS A DOMINANT IMMUNOMODULATORY PATHWAY ASSOCIATED WITH DISTINCT TUMOR MICROENVIRONMENT FEATURES IN A SUBSET OF NSCLC

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Background HLA-E is a non-classical HLA molecule that can engage the heteromeric inhibitory receptor NKG2A/CD94 to suppress T-cell/NK-cells. Blockade of NKG2A in combination with other immunostimulatory antibodies shows encouraging clinical activity in a subset of patients with locally advanced non-small cell lung cancer (NSCLC). Despite its possible clinical relevance, the levels, spatial distribution and biomarker potential of the HLA-E/NKG2A pathway in NSCLC remain poorly understood.

Methods Using multiplexed quantitative immunofluorescence (mQIF), we simultaneously measured the levels of HLA-E, NKG2A protein, CD8+ T-cells and cytokeratin (CK)-expressing cancer-cells in three retrospective NSCLC cohorts represented in tissue microarrays. The mQIF analysis included compartment-based measurements based on fluorescence co-localization as well as single-cell segmentation and spatial analysis. The first two cohorts included baseline tumor samples from patients with stages I-IV NSCLC treated with non-immunotherapy regimens (Cohort #1, n=138; Cohort #2, n=248). The third cohort (Cohort #3, n=23 pairs) included paired biopsies before and after chemotherapy +/- radiotherapy in patients with locally advanced NSCLC. Associations between the markers with clinicopathologic variables and outcomes were studied.

Results 94% of NSCLCs showed detectable expression of HLA-E and 98% of NKG2A, but the levels were highly variable across cases. HLA-E protein was predominantly expressed in CK+ cancer cells and NKG2A was higher in (nonmalignant) CK- stromal cells. The levels of the markers were positively associated across the cohorts. Elevated HLA-E or NKG2A were associated with higher local CD8+ T-cell infiltration and longer overall survival, but only HLA-E was independent from CD8+ TILs in multivariable analysis (Cohort #1, HR= 0.16 [95% CI: 0.022 to 0.89]; Cohort 2, HR= 0.074 [95% CI: 0.0042 to 0.87]). No consistent association between the marker levels and major clinicopathologic variables was found. Notably, NKG2A+ immune cells were located more distant from HLA-E-expressing than from HLA-E-negative cancer-cells.

Conclusions The HLA-E/NKG2A pathway is expressed in a large fraction of NSCLCs with a distinct expression pattern in tumor and non-tumor/immune cells. Elevated expression of HLA-E and NKG2A occurs in tumors with increased local adaptive anti-tumor responses and is associated with better outcomes and distinct spatial tumor microenvironment features. The levels and spatial distribution of HLA-E and NKG2A proteins are unaffected by chemoradiotherapy. Collectively, our results support that the HLA-E/NKG2A is a dominant immunomodulatory pathway in a subset of NSCLC with prominent biomarker and therapeutic potential.

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