107 TUMOR SPECIFIC MHC-I EXPRESSION DETERMINES THE LOCAL IMMUNE MICROENVIRONMENT IN BREAST CANCER

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Background Tumors employ various immune escape mechanisms, including downregulation of major histocompatibility complex I (MHC-I) expression, to avoid T cell-mediated antitumor immunity. Although complete MHC-I loss is possible, most tumors express MHC-I in a heterogeneous manner, with a mix of MHC-I high, mid, and low expressing tumor cells. However, the intratumor MHC-I heterogeneity and its impact on the immune microenvironment still require further study. The goal of this study is to investigate MHC-I expressional heterogeneity in breast cancer and characterize the immune landscape, with a focus on CD8 T cells, which target MHC-I expressing tumor cells, and NK cells, which target MHC-I negative/low tumor cells, in a spatial manner within the tumor microenvironment.

Methods We performed quantitative immunofluorescence for MHC-I, CD8, CD56 (NK cell marker), and pan-cytokeratin on breast cancer tumors (n=314) from diverse subtypes to obtain single-cell resolution MHC-I expression and spatial information of tumor and immune cells. Ripley's K function was used to analyze the spatial distribution of MHC-I high, mid, and low expressing tumor cells. We also performed density-based clustering to arrange neighboring tumor cells into clusters and subsequently examine the local immune cell infiltration.

Results All clinical breast cancer subtypes showed high variability in MHC-I expression, with triple-negative breast cancer (TNBC) having the highest MHC-I expression and the largest percentage of tumors with multimodal MHC-I expression (consisting of MHC-I high, mid, and low expressing tumor cells). Both MHC-I high and low expressing tumor cells, especially those in TNBC, tend to cluster and create tumoral MHC-I hot and cold spots. Meanwhile, the MHC-I high-expressing stromal cells and CD8 T cells clustered with tumoral MHC-I hot spots, while MHC-I cold spots exhibited the lowest lymphocyte infiltration and clustered with MHC-I low-expressing stromal cells. Interestingly, heterogenous MHC-I tumor clusters (those with mixed high and low expressing cells) had the highest levels of infiltrating NK cells.

Conclusions Our work reveals the heterogeneity of MHC-I expression among different breast cancer subtypes. TNBC, the immune checkpoint inhibitor (ICI)-sensitive subtype, is characterized by the highest MHC-I expression and well-defined MHC-I hot and cold spots. Additionally, the local immune landscape around MHC-I hot, cold, and heterogeneous clusters are significantly different. Increased NK cell infiltration in areas where tumor cells heterogeneously express MHC-I was also consistent with our preclinical heterogeneous MHC-I mammary tumor model. Those results suggested that immunotherapy-resistant, MHC-I heterogeneous tumors may be sensitized by combining an NK cell activation drug, such as anti-NKG2A, with already-available ICIs.

Ethics Approval Samples involved in this study are under IRB030747 and INEN 10–018

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