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Abstract 1139: Unravelling tumor heterogeneity in patients with HER2-low hormone receptor-positive breast cancer using spatial transcriptomics **FREE**

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Abstract

Background: The current binary distinction between HER2-positive and HER2-negative breast cancer (BC) has recently been challenged by the emergence of the HER2-low entity. Antibody-drug conjugates targeting HER2 have shown efficacy in both HER2-positive and HER2-low BC, while some preliminary evidence showed efficacy also in patients with HER2-zero BC. Here, by combining spatial transcriptomics (ST) and morphological annotation, we aimed to investigate the inter- and intra-tumor heterogeneity of ERBB2 expression in relation to breast cancer IHC subtypes.

Methods: We performed ST (Visium 10X Genomics) on frozen tumor samples from patients with hormone receptor positive (HR+) ductal BC with HER2 IHC staining and FISH. Hematoxylin/eosin slides were morphologically annotated integrating manual and machine learning-based approaches reaching single-cell resolution (QuPath software). The relative histomorphological categories composition of each spot across the ST slide was computed as percentage of pixels. Spots were defined as tumoral if the percentile of pixels in that spot surpassed the 80th percentile of all the tumor spots in the cohort.

Results: Our cohort consisted of 56 HER2-zero (IHC 0), 30 HER2-low (IHC 1+) and 20 HER2-positive (IHC 2+/FISH positive or IHC 3+) samples. HER2-zero samples contained a significantly higher percentage of acellular stroma spots compared to HER2-low (pvalue=0.04), while no other morphological annotation showed a difference, including tumor spots. Only tumor spots were retained for downstream analysis. A difference in the ERBB2 gene expression was found at the spot level, with a higher expression in HER2-low samples compared to HER2-zero samples (median expression 0.4, 0.7 and 3.1 in HER2-zero, HER2-low and HER2-positive, respectively). Inter-sample heterogeneity was observed, with 27% of the HER2-zero samples having equal or higher mean ERBB2 expression than the mean ERBB2 expression of the HER2-low cohort. Variability within individual samples was observed, revealing two peaks in ERBB2 expression, one characterized by low levels and the other by medium-high levels. This pattern was frequently observed in samples classified as HER2-zero and HER2-low, indicating the existence of tumor spots with diverse ERBB2 expression.

Conclusions: Our results revealed inter- and intra-tumor heterogeneity of ERBB2 expression in HER2-zero and HER2-low BC. The use of spatial transcriptomics can provide more details of the spatial distribution of ERBB2. Further validation is warranted.

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