Spatially Resolved HER2 and AR in Prostate Cancer Highlight HER2 as a Distinct Therapeutic Target

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Background: Prostate cancer (PC) begins as a localized hormone-dependent tumor and is prone to metastatic disease which initially responds to suppression of androgen signaling through androgen deprivation therapy; however, relapse is inevitable, leaving few options for men with advanced metastatic PC. Via several known pathways, as well as others yet to be determined, androgen receptor (AR) target genes are re-expressed during this course of treatment which stimulates PC cell survival, proliferation, and prostate-specific antigen secretion. For this reason, a promising area of investigation focuses on inhibiting androgen-independent signaling pathways—such as human epidermal growth factor receptor 2 (HER2/*ERBB2*)—that promote metastasis. We recently described the role of non-androgenic biomarker human epidermal growth factor receptor 2 (HER2) in PC and appealed for deeper investigation in diverse populations. HER2 is a well-characterized oncogenic driver in multiple cancer types, including PC. The higher prevalence of HER2 overexpression among Black men with PC has only recently come to light, while differences in AR expression and function in Black men has been more well-described. In this study, we utilized spatial transcriptomics to evaluate basal HER2 and AR expression in a racially diverse patient-derived xenograft (PDX) model as well as immunofluorescence to evaluate changes in HER2 and AR induced with HER2 drug targeting in a diverse panel of PC cell lines.

Methods: To resolve the spatial dynamics of *ERBB2, AR,* and other relevant gene expression in PDXs, we utilized the 10x Genomics Xenium *In Situ* spatial transcriptomics platform. Tissue sections were processed using Xenium's 377-gene Human Multi-Tissue Cancer panel, augmented with prostate-specific and *ERBB2*-related targets. To assess the effects of HER2 drug targeting on HER2 and AR expression, we performed immunofluorescence staining in treated vs. untreated LNCaP, MDA-PCa-2b, and 22Rv1 PC cell lines.

Results: Spatial transcriptomic analysis revealed that the *ERBB2* and *AR* transcript burden per tumor area were significantly higher in a PDX developed from a Black patient compared to a PDX developed from a white patient. Immunofluorescence revealed HER2–AR colocalization decreased in PC cell lines after HER2 drug targeting, suggesting disruption of HER2–AR signaling interactions.

Conclusions: These results provide evidence for crosstalk between HER2 and AR pathways in PC models and support the hypothesis that HER2 targeting impairs HER2-driven AR signaling dynamics. Dissociations between AR and HER2 suggest that HER2 serves as a distinct and targetable molecular axis. Because of the higher prevalence of HER2 reported in Black men, HER2-directed therapies have the potential to yield greater clinical impact in this high-risk population.

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