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Investigating the Proteomes and Metabolomes of HER2-positive Prostate Cancer in Response to Trastuzumab Therapy

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Background: African American (AA) men are more likely to suffer from metastatic prostate cancer (PC) and are 2.1 times more likely to die from PC than their white counterparts. Patients with PC are often treated with androgen deprivation therapy (ADT), but patients eventually experience treatment resistance and additional treatment options are limited for metastatic disease. Our lab investigates how targeting the oncogenic tyrosine kinase human epidermal growth factor 2 (HER2) could improve survival outcomes for AA men with metastatic PC. HER2 is linked to increased PC growth, metastasis, worse prognosis, treatment resistance, and increased fatty acid metabolism that contributes to oxidative stress in PC. Trastuzumab-based therapy is a standard first-line treatment for HER2-positive breast cancer but is not yet part of the treatment continuum for HER2-positive PC. Repurposing currently FDA-approved HER2-targeting agents for PC patients would drastically reduce the transition time from clinical trial to the general population thus expanding the available effective treatments, especially for AA men. Our lab has previously shown differences in cell survival response to TZ treatment in a panel of PC cell lines derived from AA and white men. However, which mechanisms and potential biomarkers are driving these differences are not yet known. We, therefore, hypothesize that HER2-positive PC cells derived from AA men may exhibit unique proteomic and metabolomic profiles in response to TZ treatment that differ greatly from PC cells derived from white men.

Methods: A panel of PC cell lines (3, white; 2 AA) was treated with either 20nM TZ or vehicle control for 72 hours and harvested. A liquid chromatography-tandem mass spectrometry LC-MS/MS bottom-up proteomics and metabolomics analyses of the PC cells from each treatment group were applied to investigate protein and metabolite abundance alterations associated with TZ treatment. Moreover, systems biology analyses were used to identify key proteins and metabolites that may provide insight into the regulated molecular pathways and processes associated with the racial differences in response to TZ that our lab previously observed.

Results: Our results indicated that more proteins showed significantly altered expression from TZ treatment in the PC cells from white men compared to the AA cells. There was little overlap observed in upregulated and downregulated proteins among the 5 cell lines in response to TZ treatment. Preliminary pathway and network analyses revealed that MYC and TP53 are key proteins regulating signal transduction, metabolism, cell cycle, and apoptosis in the white PC cells. In the AA PC cells, immune response signaling was the most impacted by TZ treatment. Interestingly, across all cell lines, the metabolic profiles showed fewer significantly altered metabolites in response to TZ treatment. We identified key metabolites: L-threonine, aceto-acetic acid, spermine, and indoleacetic acid, which regulate a wide range of signaling pathways.

Conclusions: This study of protein and metabolite abundance changes in TZ-treated PC cells derived from white and AA men helps to reveal proteins and metabolites with important pathways and regulator effects involved in PC growth and survival as well as immune response. Although this study is preliminary, the results provide novel information for a deeper insight into PC, and potential additional druggable targets for metastatic disease.

Funding Acknowledgements: NIH: TL1TR002382; NIH: UL1TR002378

Conflicts of Interest Disclosure Statement: The authors have no conflicts of interest to disclose.

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