Tumor Microenvironment-Derived NRG1 Promotes Antiandrogen Resistance in Prostate Cancer

Cancer Cell 38, 1–18, August 10, 2020,Zhang et al.

Presenter: Hsin-Yin Lin **Date/Time**: 2020/09/10 15:10 – 16:00

Commentator: Shih-Chieh LinPh.D **Location**: Ho Monto lecture hall

Background:

Androgens and androgen receptors (AR) play a pivotal role in expression of the male phenotype. androgen blockade by drugs that prevent the production of androgens and/or block the action of the AR inhibits prostate cancer growth.

Androgen deprivation therapy (ADT) is a usual first-line option for men with advanced prostate cancer.

Castrate-resistant prostate cancer (CRPC) is defined by disease progression despite androgen depletion therapy (ADT) and may present as either a continuous rise in serum prostate-specific antigen (PSA) levels, the progression of pre-existing disease, and/or the appearance of new metastases.

Cancer associated fibroblasts (CAF) are the most abundant cells of the tumor stroma and they critically influence cancer growth and progression through control of the surrounding TME.

Objective/Hypothesis:

To clarify how cancer-associated stromal cells has converged on the concept of reactive stroma and investigate the role of reactive stroma in prostate cancer and the implications for response to AR-targeted therapy.

Results:

The author first purify the human cancer epithelial cells from the mouse fibroblasts, which they named CWR22Pc-EP, and CWR22Pc-cancer-associated fibroblast and found that mixed epithelial/fibroblast cells acquired resistance to enzalutamide, the CAFs confer a pro-growth/survival signal to 22Pc-EP cells only in the setting of AR blockade.

Next using biochemical fractionation found that the resistance-promoting activity elutes in the same fractions as the HER3 phosphorylation activity and this protein called NRG-1.

In sum, the author using GSEA showed that AR transcriptional activity is not enriched by NRG1 treatment, and also found that related with clinical patient.

Conclusion:

Cancer-associated fibroblasts (CAFs) can promote antiandrogen resistance in mouse models and in prostate organoid cultures, also Neuregulin 1 (NRG1) in CAF supernatant, which promotes resistance in tumor cells through activation of HER3.

References:

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