on ALT. **Conclusion:** In summary, in a model of PCOS, BICA treatment abolished IR and BP, independent of FI, BW and HR. Prompt treatment with an AR blocker can normalize increased IR and BP triggered by androgen excess in females. Further studies need to be done to fully understand the effect of BICA in the liver in PCOS. The beneficial effect of AR blockers as a therapeutic option to improve the cardiometabolic profile in PCOS may be hampered by its liver toxicity.

Steroid Hormones and Receptors

STEROID HORMONES, NUCLEAR RECEPTORS, AND COLLABORATORS

Androgen Receptor Highjacks ErbB-2 Nuclear Function to Induce Triple Negative Breast Cancer Growth

Agustina Roldán Deamicis, MSc[1], Robert H. Oakley, PhD[2], Sergio Andonegui Helguera, MSc[3], Mariela B. Lenze, MSc[1], Santiago Madera, MSc[1], Rosalia I. Cordo Russo, PhD[1], María F. Chervo, PhD[1], Roxana Schillaci, PhD[1], Cristóbal Fresno, PhD[3], John A. Cidlowski, PhD[2], Patricia V. Elizalde, PhD[1], Cecilia J. Proietti, PhD[1].

[1]Instituto de Biología y Medicina Experimental (IBYME) - CONICET, Ciudad Autónoma de Buenos Aires, Argentina, [2]NIEHS/NIH, Durham, NC, USA, [3]Instituto Nacional de Medicina Genómica (INMEGEN), Ciudad de México, Mexico.

Triple negative breast cancer (TNBC) has poor prognosis and neither established biomarkers nor therapeutic targets. On the one hand the androgen receptor (AR), a steroid hormone receptor (SR) which is expressed in 10-53% of TNBC and proved to be critical for BC proliferation, has been proposed as a new target in TNBC. On the other hand, we and others have shown that membrane ErbB-2 migrates to the nucleus (nuclear ErbB-2, NErbB-2) where it binds DNA at HER-2 associated sequences (HAS) to regulate BC proliferation and migration. Since we have previously shown a functional interplay between growth factors and SR signaling pathways in BC, we propose the existence of an interaction between AR and ErbB-2 which is involved in NErbB-2+/AR+ BC growth. The experimental model used was the human TNBC cell line MDA-MB-453 which displays high expression levels of AR and NErbB-2. By Western Blot (WB) we found that dihydrotestosterone (DHT) treatment for short times (minutes) did not regulate ErbB-2 phosphorylation status at residues Tyr1221/1222 and 1248 which were constitutively activated. However, DHT led to an increase in ErbB-2 phosphorylation at residue Tyr877 which we have proved to be required for ErbB-2 nuclear migration. The latter effect was blocked by the AR antagonist enzalutamide (enza). Blockage of Src activity with dasatinib inhibited DHT-induced ErbB-2 phosphorylation at Tyr877. By Immunofluorescence and confocal microscopy analyses and subcellular fractionation studies we demonstrated that DHT induced ErbB-2 nuclear migration which was inhibited by enza. By chIP we found that DHT induced ErbB-2 recruitment to a HAS site in ERK5, a gene involved in BC proliferation, and to a HAS site in FKBP5, a classical AR responsive gene. By WB we demonstrated that transfection with an ErbB-2 mutant which is unable to translocate to the nucleus and functions as a dominant negative inhibitor of ErbB-2 nuclear migration (hErbB-2ΔNLS), inhibited FKBP51 up-regulation by DHT. Finally, by microarray and bioinformatics analysis we identified 315 differentially expressed genes (DEGs) in the presence of DHT and NErbB-2 eviction. Enrichment analyses showed that the DEGs belonged to the immune response and interferon pathways. Kaplan-Meier analysis revealed that the expression of 6 genes was significantly associated with overall survival in TNBC patients from the METABRIC cohort: CXCL10, TAP1, STAT1, NMI, HLA-A and NLRC5. Multivariate Cox regression analysis identified the combined expression of the 6 genes as an independent predictor of better clinical outcome in TNBC (HR: 0.56, 95% CI 0.38-0.82, P = 0.003). In conclusion, our findings evidence that DHT-activated AR induces Src-mediated ErbB-2 rapid activation and its migration to the nucleus where it binds to HAS sites in the DNA. Moreover, based on the DEGs of NErbB-2 eviction in presence of DHT we identified a gene signature associated with favorable outcome in TNBC.

Steroid Hormones and Receptors

STEROID HORMONES, NUCLEAR RECEPTORS, AND COLLABORATORS

AR Is Not an Independent Marker for TNBC: The Lesson We Learn From Two PDX Models

Xiaoqiang Wang, MBBS. Ph.D. MB (ASCP)[1], Karineh Petrossian, Ph.D.[1], Miao-Juei Huang, Ph.D.[1], Kohei Saeki, DVM, Ph.D.[1], Noriko Kanaya, DVM, PhD[2], Gregory Chang, BSc[1], Somlo George, MD.[1], Shiuan Chen, PhD[3].

[1]CITY OF HOPE NATIONAL MEDICAL CENTER, Duarte, CA, USA, [2]Beckman Research Institute City of Hope, Duarte, CA, USA, [3]Beckman Research Institute, Duarte, CA, USA.

Extensive efforts, through cell line-based models, have been made to characterize the androgen receptor (AR) signaling pathway in triple-negative breast cancer (TNBC). However, these efforts have not yet reached a consensus with regards to the mechanism of AR in TNBC. On the other hand, patient-derived xenografts (PDXs) are generally considered more appropriate than cell line-based models for recapitulating the structural and molecular features of a patient's tumor, but only a few have been reported to be AR-positive TNBC. In our study, we identified and molecularly characterized two new, AR-positive TNBC PDX models and assessed the impacts of AR agonist (DHT) and antagonist (enzalutamide) on tumor growth and gene expression profiles by utilizing immunohistochemistry (IHC), western blots, and RNA-Seq and TNBC subtyping analyses. Two PDX models, termed TN1 and TN2, were derived from two grade 3 TNBC tumors, each containing 1~5% of AR positive tumor cells. DHT activated AR in both PDX tumors by increasing AR nuclear localization and protein levels. However, the endpoint tumor volume of DHT-treated TN1 was 3-folds smaller than that of non-treated TN1 tumors. Conversely, the endpoint tumor volume of DHT-treated TN2 was 2-folds larger than that of non-treated TN2. Moreover, enzalutamide failed to antagonize DHT-induced tumor growth in TN2. The RNA-Seq analyses revealed that DHT suppressed gene expression in TN1 (961 down-regulated genes versus 149 up-regulated genes), while the