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able. Growing evidence suggests that chemotherapy-resistant BC cells with stem-like properties (CSC) may repopulate the tumor. Therefore, therapies that target the CSC in combination with chemotherapy might prevent tumor recurrence. Androgen Receptor (AR) is expressed in at least half of all TNBC. AR inhibition decreases CSC *in vitro* and tumor initiation i*n vivo*. RUNX1 is regulated by AR in prostate cancer. In TNBC patients, RUNX1 protein levels correlate with poor prognosis. Our group has shown that RUNX1 promotes TNBC cell migration and regulates tumor gene expression, such as the oncogene *RSPO3*. Also, by RUNX1 ChIP assays, we found SOX4 as a potential target gene. We hypothesized that RUNX1 is regulated by AR and that both may work together in TNBC CSCs to promote persistence and disease recurrence following chemotherapy. Here we show that, in MDA-MB-453 cells, RUNX1 expression is upregulated by dihydrotestosterone, an AR agonist, and that this effect is blocked in the presence of Enzalutamide (AR antagonist). ChIP-seq experiments revealed AR binding to RUNX1 regulatory regions, suggesting direct regulation. RUNX1 expression is increased in a CSC-like experimental model and responds to AR activity. Inhibition of RUNX1 transcriptional activity by AI-10-104 (a synthetic drug) reduced the expression of the CSC marker SOX4. Interestingly, this inhibition drives a reduction of MDA-MB-453 and BT-549 cell proliferation and enhanced paclitaxel sensitivity. It was reported that AR inhibition combined with chemotherapy results in a more effective outcome than chemotherapy alone *in vitro* and *in vivo*. In sum, RUNX1 inhibition may also be an attractive target to potentiate the anti-tumor effect of AR inhibition, specifically in the slow growing CSC-like populations that resist chemotherapy and lead to metastatic disease.

501. (507) **VITAMIN D RECEPTOR AND PACLITAXEL IN TRIPLE NEGATIVE BREAST CANCER: IS THERE A LINK BETWEEN THEM?**

Josefina Alejandra Guevara[1], Agustina Ibarra[1], Alfredo Quevedo[2], Eliana Noelia Alonso[1], Georgina Pamela Coló[1], María Marta Facchinetti[1], María Julia Ferronato[1*], Alejandro Carlos Curino [1]

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Paclitaxel (PTX) is an antitumor agent employed in the treatment of Triple-Negative Breast Cancer (TNBC). TNBC expresses Vitamin D Receptor (VDR), a member of the nuclear receptor superfamily. The aim of this work was to investigate the involvement of VDR in the antitumor action of PTX in TNBC cells. To this end, viability assays by crystal violet staining were performed in murine 4T1 TNBC cells and in 4T1 stably expressing a shRNA against VDR (4T1 shVDR), treated with PTX (10 nM) or vehicle. Also, cell cycle was studied by flow cytometry. Cellular studies were complemented with in silico analyses including molecular docking and molecular dynamics (MD) simulations to describe the pharmacodynamic interaction between PTX and VDR. The results show that PTX reduced the viability of 4T1 wild type cells ($p<0.001$). These viability effects were lost in 4T1 shVDR cells which display approximately 53% of VDR levels with respect to control cells. Cell cycle analysis of 4T1 wild type and 4T1 shVDR cells treated with PTX showed that the chemotherapy causes an increase in the percentage of cells in sub G0/G1 phase compared to vehicle-treated cells. However, this PTX effect was significantly higher in wild type than in VDR-silenced cells (13.72 ± 2.37% vs 6.18 ± 1.07%, $p<0.001$). Docking and MD studies showed that PTX was not able to bind to the classical ligand-binding pocket of VDR. However, an exhaustive search of allosteric sites identified its stable binding to a cavity adjacent to the activating factor 2 (AF-2) region. MD studies verified a conformational restraint on AF-2, which triggers transcriptional and antitumor effects. Furthermore, a potential cooperativity in the interaction with VDR between PTX and the natural ligand of the receptor was observed. Altogether, these results suggest that PTX could interact with VDR to display its antitumor effects in TNBC by its binding in an alternative site to that of the classical VDR agonists.

502. (509) **NOVEL HISTAMINE H_3 RECEPTOR ANTAGONISTS WITH POTENT ANTINEOPLASTIC PROPERTIES AS TARGETED DRUG THERAPY FOR BREAST CANCER**

Mónica A. Táquez Delgado[1], Melisa B. Nicoud[1], Ignacio Ospital[1], Michelle F. Corrêa[2], Gustavo A. B. Fernandes[2], Diego Martinel Lamas[1], João P. S. Fernandes[2], Vanina A. Medina[1].

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We have reported the expression of the histamine H_3 receptor (H_3R) in human benign and malignant lesions, and cell lines derived from human mammary glands. Its expression is highly correlated with proliferation in breast cancer specimens.

In this work, we aimed at investigating the potential antitumoral activity of 4 novel H_3R antagonists, 1-(2,3-dihydro-1-benzofuran-2-yl) methylpiperazines (LINS01 compounds), which showed excellent selectivity and high affinity for the human H_3R.[1,2] Cell viability and proliferation were assessed by cell titer blue assay and colony formation in human MDA-MB-231 and murine 4T1 triple negative breast cancer cells. Cell apoptosis was assessed by Annexin V staining and flow cytometry, while cell migration was evaluated by wound-healing assay and transwell system. The lipid accumulation was assayed by flow cytometry using Nile-red staining.

Results indicate that compounds LINS01022, LINS01023, LINS01009, LINS01010 (0.1-100 μM) produced a concentration-dependent inhibition on cell growth. The highest responses were observed for LINS01022 and LINS01023, showing an IC_{50} in the cell viability assay of 82.7 and 78.2 μM for MDA-MB-231 cells, and 87.0 and 59.2 μM for 4T1 cells. LINS01022 and LINS01023 (25-50 μM) induced cell apoptosis (4 to 7 fold-increase) and differentiation (2 to 3 fold-increase), while suppressed cell migration in both cell lines ($P<0.01$).

The allylpiperazines LINS01022 and LINS01023 exhibited better antiproliferative and proapoptotic effects together with a higher affinity constant for the H_3R than their corresponding methylpiperazine analogues LINS01009 and LINS1010, respectively.

These effects were not observed with the selective H_3R agonist, (*R*)-alpha-methylhistamine.

In conclusion, this study demonstrates that the H_3R is involved in the regulation of cell growth and progression, offering novel therapeutic potentials for H_3R antagonists.

[1]Correa et al. *Front Pharmacol* **2017**,*8*,825

[2]Correa et al. *Bioorg Med Chem* **2021**,*30*,115924

503. (510) **HIF-1α REGULATES TUMOR PROGRESSION IN A HUMAN EPITHELIAL OVARIAN CANCER MODEL**

España De Marco María José[1], Irusta Griselda[1], Tesone Marta[1], Pérez Piñero Cecilia[2].

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Ovarian cancer is the seventh most common cancer in women and the eighth cause of cancer death. The treatment of this disease has been the same for the past decades, and the development of new drugs is needed. Hypoxia is a common characteristic of solid tumors, usually associated with a more aggressive phenotype. The main transcriptional factor involved in this process is Hypoxia Inducible Factor 1 alpha (HIF-1α).

The present work aimed to study the effect of Acriflavine (ACR), a specific HIF-1α inhibitor, on a human epithelial ovarian cancer model (SKOV3), both *in vivo* and *in vitro*. For the *in vitro* experiments, we