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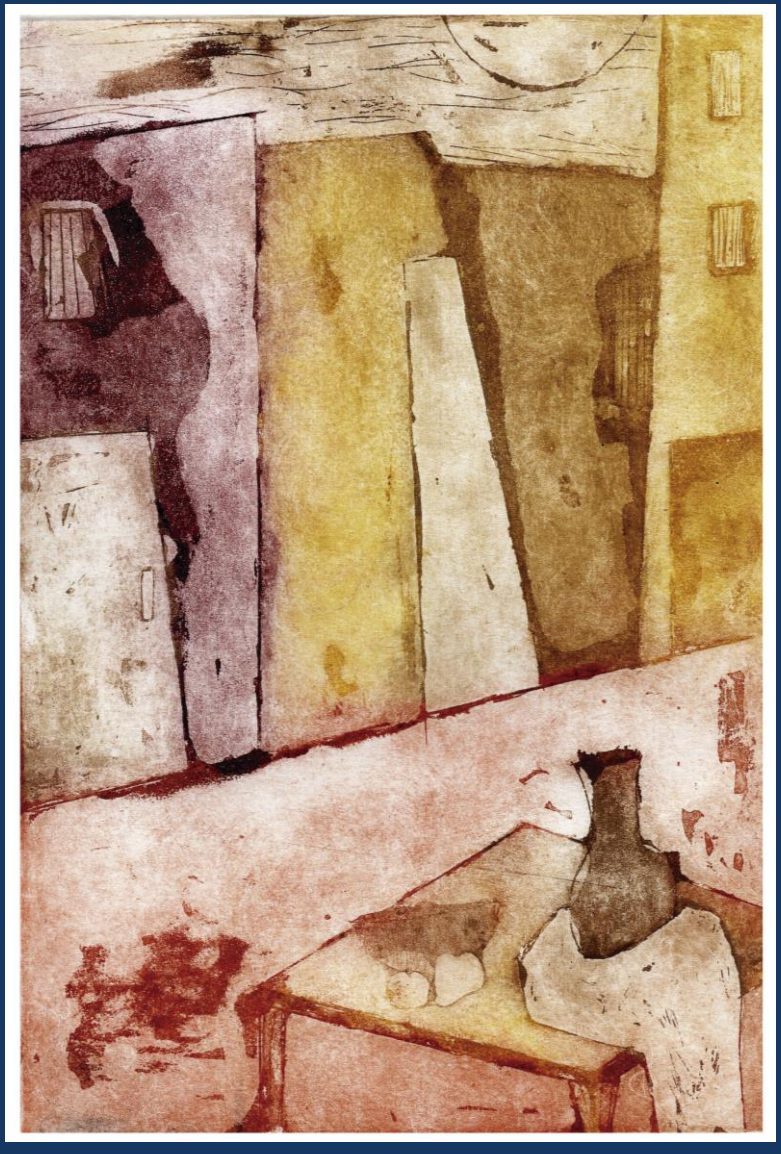

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La Tapa (Ver pág. 4)
Atardecer en la tarde
Antonella Ricagni

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VI Reunión Científica Regional de la Asociación Argentina de Ciencia y Tecnología de Animales de Laboratorio (AACyTAL)

con la participación de
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to elucidate if such forms of HO-1 impacts on head and neck cancer cells behavior. We established the FL-HO1 and t-HO1 overexpressing HN13 cells. We evaluated cell viability by crystal violet method, cell cycle progression by propidium iodide staining and flow cytometry, and cell migration by wound healing assay. In addition to our previous results using hemin, we found that 80 µM hemin increased cell number in S- ($p<0.001$) and G2/M ($p<0.001$) phases and diminished cell number in Go/G1 phase ($p<0.001$) at 72h. We also found that hemin delayed cell migration ($p<0.01$) respect to control. On the contrary, at same conditions, hemin failed to increase cell viability ($p>0.05$) neither alters cell cycle progression ($p>0.05$) in the normal keratinocyte cell line, HaCaT. By a genetic approach, we found that FL-HO1 HN13 cells have a higher growth rate ($p<0.001$) than its control and cell cycle progression is as similar as ($p<0,001$ vs control) it was observed with hemin treatment. However, FL-HO1 failed to alter migratory capacity ($p>0.05$). We also found that t-HO1 expression impaired HN13 cell viability ($p<0.01$ vs. FL-HO1 HN13) and induces a Go/G1 arrest ($p<0.01$) and a diminished cell number in SubGo ($p<0.01$) and S- ($p<0.05$) phases. Also, we found that t-HO1 expression delayed cell migration ($p<0.001$) respect to FL-HO1 HN13. In conclusion, our results show that head and neck cancer cells survival, cell cycle progression and migration capacity depends on predominant HO-1 form.

0407 - NOVEL CALCITRIOL ANALOGUES EM1 AND UVB1 AGAINST AGGRESSIVE BREAST CANCER CELLS AS A MONOTHERAPY OR IN COMBINATION WITH PACLITAXEL.

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Abstract/Resumen: Despite chemotherapy remaining as a primary therapeutic option for aggressive breast cancer (BC), its effectiveness is limited by intrinsic or acquired resistance and associated adverse effects. Therefore, new therapeutic strategies are needed. Previously, we demonstrated that the calcitriol analogue EM1 decreases the viability, migration and invasion of the 4T1 triple-negative BC (TNBC) cells. Additionally, we reported that UVB1, another calcitriol analogue synthetized by our group, reduces the viability of cells derived from the TNBC - Patient-Derived Xenografts (PDX). Hence, the aim of the present study was to continue evaluating the antitumoral effects of the calcitriol analogues EM1 and UVB1 on aggressive BC cells, alone or in combination with low concentrations of Paclitaxel (PTX). We found a synergistic effect by combining EM1 or UVB1 with non-effective PTX concentrations on viability of 4T1 cells. The resulting Combination Index values of Chou & Talalay method were 0.80059 and 0.13491 for EM1-PTX and UVB1-PTX combinations, respectively. In addition of our previous result on 4T1 cell migration, EM1 displayed antimigratory effects on MDA-MB-231 TNBC cell line ($p<0.001$). In contrast, UVB1 had no effect on these cells. However, interestingly, the combination of the analogues with non-effective concentrations of PTX over 4T1 cell migration displayed a better effect than drugs alone (EM1-PTX: $p<0.05$; UVB1-PTX: $p<0.001$). Finally, a pilot in vivo assay was conducted to test the sensitivity of the TNBC-PDX410 to UVB1. A reduction in in vivo tumor volume was detected after 18 days of UVB1 treatment at 40 µg/kg of body weight administrated three times a week ($p<0.05$). Altogether, these results suggest the potential use of these vitamin D analogues as antitumor agents, alone or as a complement to conventional chemotherapy.

0408 - ANTITUMORAL EFFECTS OF PLEUROTUS OSTREATUS I-FRACTION IN BREAST CANCER

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Abstract/Resumen: Mushrooms are considered as "small pharmaceutical factories" producing hundreds of bioactive compounds, many of which have shown to exert antitumoral activity in different types of cancer. Argentina has a high mushrooms diversity and important scientific-technological development applied to its cultivation. However, the antitumoral phytotherapeutic potential of edible mushrooms cultivated in our country has not yet been considered. In this context, the purpose of the current study is to determine the antitumoral activity in breast cancer of Pleurotus ostreatus I-Fraction, an extract of water-soluble polysaccharides obtained from fruiting body, initially evaluating its potential immuno-independent antitumoral activity. To achieve the proposed objective, we employed a murine mammary adenocarcinoma 4T1 cells line and performed cell viability assays by colorimetric assay with crystal violet, cell cycle analysis by flow cytometry, and wound healing assay. We found that P. ostreatus I-Fraction at concentration from 2.5 mg/mL and ranging from 1.0 to 2.5 mg/mL decreased the viability of 4T1 cells in a concentration-dependent manner, at 24 hours and 48 hours respectively ($p<0.001$). These results also demonstrate a time-dependent effect of I-Fraction on 4T1 cells viability. In addition, P. ostreatus I-Fraction (2.5 mg/mL, 48 h) increased the number of 4T1 cells in the subG0/G1 phase (I-Fraction= 9.05 vs. vehicle= 2.3 %, $p<0.001$) and decreased those in the G0/G1 phase, compared to vehicle (I-Fraction= 42.3 vs. vehicle= 48.77 %, $p<0.001$). These results suggest that I-Fraction decreases 4T1 cell viability through an induction in cell death, without affecting cell cycle progression. By another hand, we found that I-Fraction decreased migratory capability of 4T1 cells at 13 h of treatment, compared to vehicle ($p<0.01$). In conclusion, these results demonstrate the antitumor activity of Pleurotus ostreatus I-Fraction on breast cancer cells.

0409 - P300 INVOLVEMENT IN METASTATIC PROCESS OF TRIPLE NEGATIVE BREAST CANCER

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Abstract/Resumen: Triple negative breast cancer (TNBC) are a heterogeneous group of tumors which lack specific molecular targets. Therefore, it is necessary to investigate potential tumor markers for this subtype of BC. Recent studies indicate that p300 has a pro-metastatic role in BC and we have previously shown that inhibition of p300 decreases cellular migration and invasion in a TNBC cell line. Therefore, in this work we aimed to analyze the expression and localization of p300 and its association with markers of tumor progression and clinic-pathological parameters in human TNBC. Also, we investigated the molecular mechanisms through which p300 inhibition impaired the processes previously mentioned. In TNBC biopsies (n= 45), we found that higher levels of cytoplasmic p300 correlates with lower tumor stages and a better overall patient survival (IHC, $p<0.05$). In TNBC (MDA-MB-231) and hormone-independent BC (LM3) cell lines, the genetic silencing of p300 induced an increase in the levels of

membrane E-cadherin, a decrease of nuclear ß-catenin and in the number of stress fibers compared with the control (IF, $p<0.05$). In a mouse xenograft model of MDA-MB-231 we found an increase in E-cadherin and a decrease in nuclear ß-catenin expression (IHC, $p<0.05$) in the tumors of animals injected with VV59, a specific pharmacological inhibitor of p300. Also, in such group of mice, we found a significant reduction in the number of lung metastases respect to control group ($p<0.05$). Altogether these results demonstrate an antitumor role for p300 inhibition or cytoplasmic translocation in TNBC.

0415 - TUMOR MICROENVIRONMENT: EFFECT OF METRONOMIC CHEMOTHERAPY WITH CYCLOPHOSPHAMIDE (CY) AND LOSARTAN (LOS) ON M-406 MURINE MAMMARY ADENOCARCINOMA

Mónica Carolina GRILLO | Cintia KAUFMAN | M. Virginia BAGLIONI | Antonela DEL GIÚDICE | Viviana Rosa ROZADOS | Olga Graciela SCHAROVSKY | María Jose RICO | Leandro E. MAINETTI

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Abstract/Resumen: Metronomic chemotherapy (MCT) refers to the chronic, equally spaced, delivery of low doses of chemotherapeutic drugs, without extended interruptions. Drug repositioning (DR) in oncology refers to the use of drugs originally formulated for other indications that showed antitumor potential. CY is an alkylating drug with toxic action on proliferating cells. LOS is an antagonist of angiotensin II receptor, used to treat hypertension. Tumor microenvironment is constituted by genetically stable cells that surround and feed the tumor, favoring sustained growth, invasion and metastasis. It was previously shown that MCT with CY+LOS inhibited M-406 growth and increased mice survival without general toxic effects. Our objective was to study the effect of metronomic CY+LOS treatment, on M-406 tumor microenvironment. CBi female mice were challenged s.c. with M-406 (day 0) and distributed on day 6, into 4 groups (n= 6-7/group). GI: Control, non-treated; GII: Treated with CY 25 mg/kg/day in the drinking water; GIII: Treated with LOS 150 mg/kg/day in the drinking water; GIV: Treated as GII+GIII. Mice weight and tumor volume were determined 3 times/week. When tumors reached the exponential growth phase, mice were euthanized, tumors excised and prepared for immunohistochemical analysis. Foxp3+ cells/field decreased significantly in GIV compared to GI ($p<0.05$), without showing changes in CD4+ and CD8+ lymphocytes among groups. There was a significant decrease of Ki67+ cells in GIV with respect to GI ($p<0.05$) while no modifications in apoptosis (TUNEL) were evinced. Collagen and a-SMA levels decreased in GIII and GIV, without reaching statistical significance. HIF1a+ cells/field decreased in GII and GIV groups compared to GI ($p<0.05$). In conclusion: the stimulation of the immune system, the inhibition of tumor cells proliferation and the decrease in markers of cancer associated fibroblast may be, at least in part, responsible for the therapeutic effect achieved by MCT with Cy + LOS.

0421 - MITOCHONDRIAL-DERIVED PEPTIDE HUMANIN AS A CYTOPROTECTIVE FACTOR IN BREAST CANCER CELLS

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INBIOMED- INSTITUTO DE INVESTIGACIONES BIOMÉDICAS. UBA-CONICET (1); UNIVERSIDAD NACIONAL DE LA PLATA (2)

Abstract/Resumen: We and others have previously shown that the mitochondrial-derived peptide Humanin (HN) exerts cytoprotection in normal and tumoral cells. HN can be secreted and bind to membrane receptors. Two HN receptors have been identified: (i) a trimeric receptor composed by the ciliary neurotrophic factor receptor (CNTFR), the IL27R (WSX-1) and the 130 kDa glycoprotein (gp130), and (ii) the formyl peptide receptor-like 1 (FPRL-1 or FPR2). We have previously observed that exogenous HN facilitates tumor progression and chemoresistance in experimental triple negative breast cancer (TNBC). Here we performed bioinformatics analysis of transcriptomic databases to assess the expression of mRNA of HN and its receptors in breast cancer specimens. We found expression of HN mRNA in normal human breast tissue and breast tumors specimens of all types, i.e. luminal A, luminal B, HER2+, and TNBC. HN receptors mRNA were also detected in human breast tumors. While the expression of the trimeric receptor subunits was similar in all subtypes of breast tumors, FPR2 expression was highest in TNBC (*$p<0.05$, ANOVA follow by Tukey test). When we assessed the effect of HN on the response of HER2+ breast tumor cells, we found that HN (20 µM) inhibited the cytotoxic effect of Doxorubicin (50 µM), as assessed by MTT (ANOVA, *$p<0.05$) and TUNEL (x^2 test *$p<0.05$). We next evaluated the effect of HN on the secretion of immunosuppressive interleukin-10 (IL-10) and the production of angiogenic factors in HER2+ and TNBC cells. HN (10 µM) decreased IL-10 release from LM3 cells. Conditioned media of LM3 and 4T1 cells that were incubated with HN (10 µM) inhibited the proliferation of endothelial cells EA.hy926 (ELISA BrdU, *$p<0.05$, ANOVA).Our results suggest that the protumoral action of HN may result from a direct cytoprotective action on breast tumor cells rather than being mediated by an effect on the tumor immunosuppressive phenotype or proangiogenic capacity.

0425 - EFFECT ON THE TUMOR MICROENVIRONMENT OF METRONOMIC CHEMOTHERAPY WITH CYCLOPHOSPHAMIDE (CY) AND LOSARTAN (LOS) IN A MURINE MODEL OF MAMMARY ADENOCARCINOMA

Cintia KAUFMAN | Mónica Carolina GRILLO | Maria Virginia BAGLIONI | Antonela DEL GIÚDICE | Viviana Rosa ROZADOS | Olga Graciela SCHAROVSKY | María Jose RICO | Leandro E MAINETTI

INSTITUTO DE GENÉTICA EXPERIMENTAL. FACULTAD DE CIENCIAS MÉDICAS. UNIVERSIDAD NACIONAL DE ROSARIO

Abstract/Resumen: Metronomics, refers to all anticancer treatment regimens combining metronomic chemotherapy (chronic, low dose, no extended rest periods drug administration) and drug repositioning (the use of drugs originally formulated to other indications that showed antitumor effect). CY (drug with cytotoxic action on proliferating cells) and LOS (angiotensin II receptor antagonist, used to treat hypertension) were used in a metronomics schedule. We have demonstrated that the administration of metronomic CY+LOS in the triple negative M-234p mammary adenocarcinoma tumor model, inhibited tumor growth, increasing the survival rate without toxicity. Our aim was to study the effect of MCT with CY+LOS in M-234p tumor microenvironment. Female BALB/c mice were challenged s.c. with M-234p (day 0) and on day 6 divided in 4 groups (n= 6-10/group). GI: Control, with no further treatment; GII: Treated with CY 25 mg/kg/day in the drinking water; GIII: Treated with LOS 200 mg/kg/day in the drinking water; GIV: Treated as GII+GIII. Mice were weighted and tumor volume measured 3 times/week. When tumors were exponentially growing, they were excised and used for immunohistochemistry and flow cytometry. GII and GIV exhibited a decreased number of HIF1a+ cells vs. GI ($p<0.001$). Stromal a-SMA (smooth muscle actin) and intratumor collagen area were smaller in GIV than in GI ($p<0.05$). At day 31, flow cytometry of tumor samples showed no differences in the number of CD4+, CD8+, IL-17+ and Foxp3+ cells among groups. At day 42, GI and GIII mice had already been euthanized and tumor volume in GIV was lower than in GII ($p<0.01$) and the number of tumor IL-17+ cells was higher and Foxp3+ cells lower in GIV than in GII ($p<0.05$, $p<0.001$, respectively). We conclude that the antitumor effect of MCT with CY+LOS could be, in part, a result of tumor