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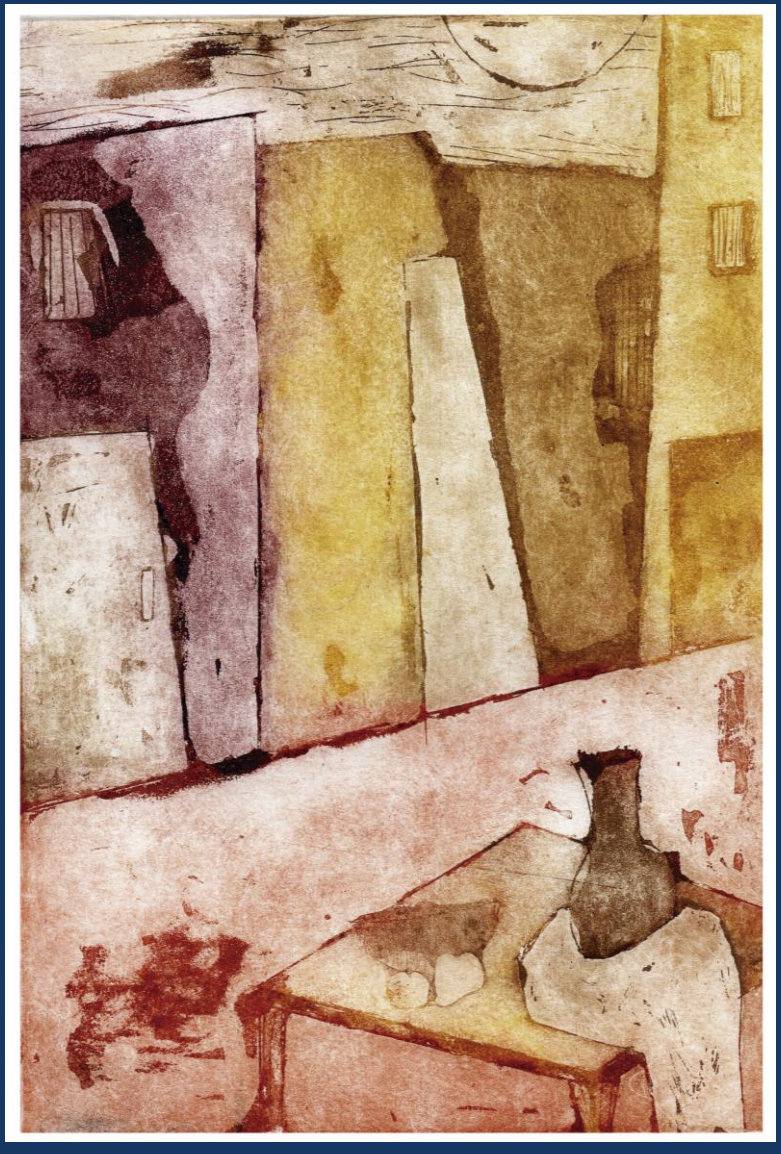

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La Tapa (Ver pág. 4)
Atardecer en la tarde
Antonella Ricagni

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IX Reunión Anual de la
Asociación Argentina de Nanomedicinas
(NANOMED-ar)

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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13 - 16 de noviembre de 2019
Hotel 13 de Julio - Mar del Plata

EDITORES RESPONSABLES

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associated to EMT by RT-qPCR, and the sensitivity to the chemotherapeutic agent Cisplatin was measured by MTS assays. Sustained exposure to analogs reduced the NE markers expression, and modulated the expression of genes associated to EMT in vitro. Furthermore, we assessed angiogenesis in vivo with Matrigel® plug modified assay in nude mice. Treatment with each analog reduced PC-3 cell-induced angiogenic response by nearly 50 % versus control. These results position AVP analogs as potential and interesting angiostatic agents, with the ability to modulate aggressiveness for CRPC, a disease with few therapeutic alternatives.

0392 - DOWNREGULATION OF MUSCARINIC RECEPTORS GENE EXPRESSION IN HUMAN BREAST CANCER CELLS REGULATES ANCHORAGE-INDEPENDENT CELL GROWTH IN VITRO AND ANGIOGENESIS IN VIVO.

Dileyvic GIAMBALVO | Adriana MARTINEZ | Alejandra NOZYCE | Lucas LASERNA | Manuel OROÑO | Maria Gabriela LOMBARDI

CENTRO DE ESTUDIOS FARMACOLÓGICOS Y BOTÁNICOS (CEFYBO), UNIVERSIDAD DE BUENOS AIRES-CONICET

Abstract/Resumen: Muscarinic receptors (M) expression, activation and signalling play important roles in regulating many cellular process and cancer progression. It has been reported that human breast cancer MCF-7 cells express muscarinic receptors M3 and M4 subtypes and its activation promotes tumoral progression. We previously reported that the silencing of both M3 and M4 in MCF-7 cells significantly reduced neovascularization capacity of tumoral cells in vivo. The aim of this work was to evaluate the specific contribution of each M receptor on different tumoral progression parameters like anchorage-independent cell growth and angiogenesis in vivo. Here, we silenced M3 or M4 subtypes in MCF-7 cells by specific RNAi. After 5 days we used the different experimental groups (siM3, siM4 and MCF-7 cells with and without carbachol (Carb, -8M)) in the following assays. Briefly, for soft agar colony assay we seeded $2X10^4$ cells of each group into medium with soft agar. After 2 weeks, the colonies larger than 60 µm in diameter were counted. We observed that cholinergic stimulation of siM cells showed a significant reduction in colony number when compared with MCF-7+Carb, however this effect was greater in siM3 cells than in siM4 cells (siM3: 99.97 ± 9.50 %, siM4: 289.4 ± 5.3 % vs. MCF-7: 509.1 ± 11.8 %; $p<0.0001$). Angiogenesis was measured by inoculation of $2x10^5$ cells in female nude mice. After 5 days, the animals were sacrificed and angiogenesis was quantified in the sites of inoculation as vessel density. We found that silencing of both M receptors decreased the neovascular response in vivo of siM cells treated with Carb compared with MCF-7+Carb (siM3: 3.6 ± 0.1, siM4: 3.7 ± 0.3 vs. MCF-7: 6.4 ± 0.7; $p<0.0001$). According to our results, M receptors expression downregulation can modulate the malignant phenotype of MCF-7 cells, having a high inhibitory effect on anchorage-independent cell growth and angiogenesis.

0686 - ADENYLATE CYCLASE GENES ARE EXPRESSED IN BASAL CELL CARCINOMA AND NORMAL SURROUNDING SKIN OF NEVOID BASAL CELL CARCINOMA SYNDROME (NBCCS) PATIENTS

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INSTITUTO DE INVESTIGACIONES MÉDICAS ALFREDO LANARI - UNIVERSIDAD DE BUENOS AIRES (1); HOSPITAL ITALIANO DE BUENOS AIRES (2)

Abstract/Resumen: NBCCS – also known as Gorlin-Goltz syndrome – is an autosomal dominant entity caused mainly by mutations in the PTCH1 gene. NBCCS is characterized by multiple basal cell carcinoma (BCC) development due to the Hedgehog (HH) pathway hyperactivation. We have previously described that the genes encoding components of the HH pathway are overexpressed in BCC and phenotypically normal skin of these patients (Martinez MF, et al. Cells, 2019). Taking into account that the HH pathway can be inhibited through proteolysis of its effectors by a cAMP-driven process that involved protein kinase A, we looked for the expression profile of the nine adenylate cyclase genes (ADCY 1 to 9). We performed quantitative RT-PCR in BCC and normal surrounding tissue (NST) of 4 NBCCS patients with PTCH1 mutations, and 3 control skin samples (CSS). We failed to detect ADCY6 mRNA in any tested samples. ADCY8 is only expressed in BCCs and the remaining ADCY genes are expressed in BCCs and NST of NBCCS patients. Any adenylate cyclase genes were expressed in the CSS. Additionally, we found a 2-fold increase in ADCY1 and a 10-fold decrease in ADCY5 mRNA levels in BCC compared to NST ($p<0.05$). These results reveal that adenylate cyclases are involved in NBCCS and suggest that the gene expression levels of cAMP pathway components could be modified directly or indirectly by the HH pathway hyperactivation. Our finding can improve the knowledge of phosphodiesterase inhibitors mechanism, another component of the cAMP pathway, in the treatment of BCCs and also be the initial study to delineate new ones.

0703 - HO1 PLAYS AN IMPORTANT ROLE IN IRON METABOLISM ALTERATION IN BREAST CANCER CELLS

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Abstract/Resumen: Heme Oxygenase-1 (HO1) catalyzes heme degradation, yielding biliverdin, carbon monoxide and iron. When iron is in excess produces oxidative stress through reactive oxygen species (ROS) generation. Since both HO1 and iron metabolism disruptions have been related to breast cancer progression, we sought to investigate how tumor cells regulate iron metabolism when HO-1 expression is altered. For this purpose, we first investigated the correlation of HO1 with several iron proteins by using in silico analyses and corroborated the strongest hits by using immunohistochemistry (IHC) performed on human biopsies (n= 33). In addition, a syngeneic model of LM3 and a xenograft model of MDA-MB-231 cells stably overexpressing HO1 were used to study these hits. We further performed in culture analyses using LM3 breast cancer cells treated with hemin (H), vehicle or the combination with an antioxidant, and studied iron storage (Prussian Blue), ROS levels (DFCA) and cell cycle progression (flow cytometry). In silico analyses showed that HO1 correlated with DMT1 (p= 9.8e-05), ZIP14 (p= 4.2e-06), Prohepcidin (p= 1.4e-12) and L-ferritin (p= 2.2e-16). In order to study the correlation between HO1 and DMT1 in breast cancer we analyzed by IHC their expression in biopsies. We observed an inverse correlation between DMT1 and HO1 expression ($p<0.05$). The IHC studies showed an increase in ZIP14 and prohepcidin expression and a slight decrease in L-ferritin and DMT1 expression in hemin-treated and HO1-overexpressing cells in both animal models. In culture studies showed that the iron storage was increased in hemin- treated LM3 cells and was associated to a decrease in cell viability ($p<0.05$), an increase in the apoptotic rate ($p<0.05$) and high ROS levels ($p<0.01$). NAC treatment reverted the apoptotic effect of H ($p<0.05$). Altogether these results indicate that HO1 induction plays a role in carcinogenesis through free iron accumulation, ROS production and oxidative stress.

0716 - BONE MARROW DERIVED MONOCYTES MEDIATE THE DELIVERY OF CONJUGATED POLYMER NANOPARTICLES IN A PLECLINICAL GLIOBLASTOMA ORTHOTOPIC MODEL