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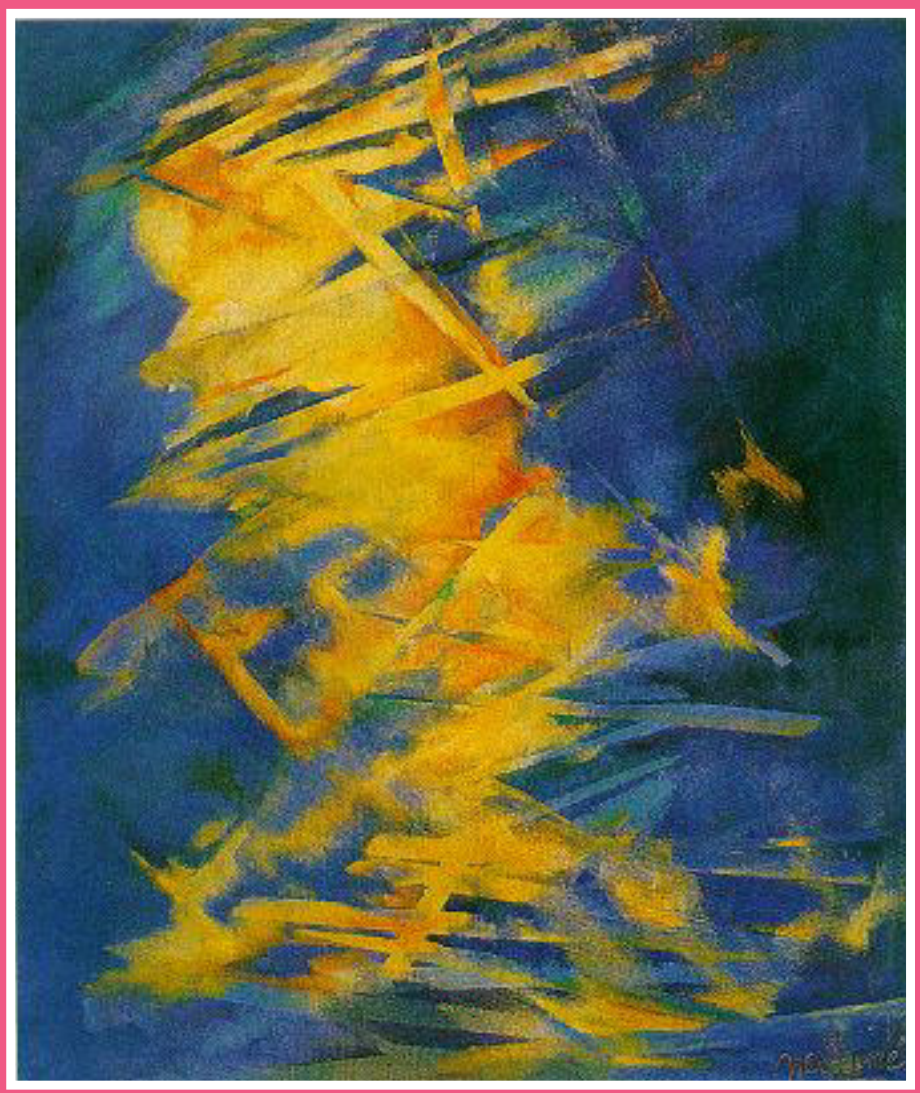

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(1787) **"TLR2 STIMULATION PROMOTES AUTOPHAGY AND MODULATES FLUDARABINE-INDUCED CELL DEATH IN CHRONIC LYMPHOCYTIC LEUKEMIA CELLS"**

Daniela Soledad Arroyo (1), Claudio Bussi (2), Javier María Peralta Ramos (2), Viviana Beatriz Heller (1), Cecilia María Rodríguez (1), Pablo Iribarren (2)
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Chronic Lymphocytic Leukemia (CLL) is a disease characterized by the clonal proliferation and accumulation of mature, typically CD5-positive B-cells within the blood, bone marrow, lymph nodes, and spleen. Leukemic transformation is initiated by alterations that impair apoptosis of clonal B-cells and the pathways engaged in programmed cell death involve several Bcl-2 family proteins. It has been described that Bcl-2–family proteins may regulate autophagy. This degradative pathway has dual role in cancer depending of the type of tumor. Therefore, autophagy can be exploited for promote survival, or cell death, as well. Whereas autophagy can be regulated by Toll like receptors (TLRs), and these receptors participate in the CLL progressive pathogenesis, we hypothesize that TLR2 activation modulate autophagy in CLL cells. This effect may influence the expression of genes and proteins involved in CLL pathogenesis. We analyzed LC3B expression in peripheral blood mononuclear cells isolated from CLL-patients. Pam3CSK4 (TLR2 ligand) induced increased LC3B II expression in CLL cells and this effect was potentiated by co-stimulation with Pam3CSK4 plus Fludarabine. Interestingly, Pam3CSK4 modulated CLL cell death induced by Fludarabine.

On the other hand, MDP (ligand for the innate immunity receptor NOD2) induced similar effects on CLL cells.

These preliminary results suggest that innate receptors may affect autophagy and leukemia cell survival.

Keywords: Toll like receptors; autophagy; Chronic Lymphocytic Leukemia

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(298) **ANTI-TUMOR ACTIONS OF PACLITAXEL PLUS CARBACOL ON HUMAN TRIPLE NEGATIVE BREAST CANCER CELLS**

Agustina Salem, Yamila Sanchez, María Elena Sales, Alejandro Español
CEFYBO-UBA-CONICET

Abstract: The administration of low doses of cytotoxic drugs alone or combined with repurposing drugs scheduled with short inter-dose intervals is called metronomic therapy (MT). MT is a new strategy in cancer treatment, since it exhibits high effectiveness and low incidence of side effects. The most aggressive type among human breast tumors is triple negative (TN), probably due to the absence of a specific target for pharmacological treatment. Here, we analyzed the effect of a combination of subthreshold concentrations of carbachol (CARB) (10^{-12}M) with paclitaxel (PX) (10^{-8}M) on MDA-MB231 cell line derived from a TN breast cancer patient during 40 h. By MTT assay we observed that the addition of 10-6M PX, a concentration similar to that used in conventional chemotherapy increased tumor cell death by 40±2% ($p<0.001$ vs. control) but also increased by 33±2% ($p<0.001$ vs. control) cell death in non-tumorigenic mammary cells MCF-10A. On the other hand, the combination of CARB with PX increased cytotoxicity by 27±3% ($p<0.01$ vs. control) without affecting MCF-10A viability. In addition, CARB plus PX reduced MDA-MB231 tumor-induced neovascularization (N°vessels/mm^2 skin) in nude mice skin (skin: 3.17±0.05; tumor: 4.14±0.23 $p<0.001$ vs. skin; tumor+CARB+PX: 3.16±0.35 $p<0.001$ vs. tumor) and the expression of vascular endothelial growth factor-A in tumor cells ($p<0.05$). Using a xenogeneic model, nude mice were inoculated with MDA-MB231 tumor cells ($3x10^6$) in the left flank and after tumor palpation, animals were treated with CARB plus. PX (i.p.). The combination significantly reduced tumor growth in relation to control (untreated mice; $p<0.001$). These results suggest that CARB plus PX at low doses could be a new strategy to treat TN breast tumors in humans.

Keywords: cancer; metronomic-therapy; angiogenesis

(1522) **ANTITUMORAL AND ANTIMETASTATIC ACTIVITY OF MAITAKE D-FRACTION IN TRIPLE-NEGATIVE BREAST CANCER CELLS.**

Eliana Noelia Alonso, María Julia Ferronato, Norberto Ariel Gandini, María Eugenia Fermento, Josefina Alejandra Guevara, Florencia Mariani, María Marta Facchinetti, Alejandro Carlos Curino
Laboratorio de Biología Del Cáncer, Instituto de Investigaciones Bioquímicas de Bahía Blanca (INIBIBB), Universidad Nacional del Sur (UNS) Conicet, Departamento de Biología, Bioquímica y Farmacia (UNS), Bahía Blanca, Argentina

D-Fraction is a proteoglucan extracted from *Grifola frondosa* (Maitake) mushroom. Previously, we reported that D-Fraction decreases breast cancer (BC) cell viability regardless of hormone receptors and HER2 status of cells. Furthermore, D-Fraction reduces tumor burden and lung metastases in a murine model with hormone-independent LM3 cells. In triple-negative (TNBC) MDA-MB-231 cells, we also demonstrated that D-Fraction decreases their migration and invasion capacity. The purpose of the current study is to identify the cellular and molecular mechanisms by which D-Fraction decreases the migratory/invasive potential of MDA-MB-231 cells. In addition, we propose to evaluate the antitumoral effect of D-Fraction in 4T1 cells, another cell line representative of TNBC subtype. By western blot, we found that D-Fraction increases E-cadherin expression in MDA-MB-231 cells compared to vehicle treatment ($p<0.05$). By immunofluorescence, we detected that D-Fraction decreases the presence of β-catenin in the cytoplasm/nucleus ($p<0.001$) and promotes its membrane localization ($p<0.01$). Also, we found that D-Fraction increases the adhesion of MDA-MB-231 cells to substrate ($p<0.05$). By zymography, we detected that D-Fraction decreases MMP-2 and MMP-9 activity by 53.59 % ($p<0.001$) and 27.31 % ($p<0.05$) respectively, compared to vehicle treatment. On the other hand, manual cell counting and WST-1 assay were performed in TNBC 4T1 cells. D-Fraction decreases the viability of 4T1 cells in a dose- and time-dependent manner ($p<0.05$). Wound healing assay demonstrated that D-Fraction decreases the migratory capability of 4T1 cells ($p<0.001$). By transwell Matrigel assay, D-Fraction reduces the invasive capability of these cells ($p<0.001$). In conclusion, our results suggest that D-Fraction decreases the viability and metastatic potential of TNBC cells: promoting an epithelial phenotype; reducing the capability of tumor cells to degrade extracellular matrix and increasing cell-substrate adhesion.

Keywords: D-Fraction, Maitake, triple-negative breast cancer, antitumoral, antimetastatic.

(1332) **CDC42 REVERTS AGGRESSIVENESS OF A TRIPLE NEGATIVE BREAST CANCER CELL LINE TROUGH METHYLATION OF ID4 PROMOTER**

Daniela Lucia Nasif, Sergio Laurito, Emanuel Campoy, María Roqué Moreno, María Teresita Branham
IHEM-CONICET

Breast cancer constitutes a group of diseases characterized by different morphologies and biological behaviors. Molecularly they can be classified as luminal A, luminal B, human epidermal growth factor receptor 2, and triple-negative breast cancers (TN); lacking ER/PR/HER2. Clinically, the TN subtype has an aggressive nature, higher rates of relapse and shorter overall survival. TN tumors affect younger patients and are more prevalent in African-American and Latin women. Cdc42 is a plasma membrane-associated small GTPase which is involved in the regulation of several cellular functions and its expression is dysregulated in several tumor types. Here we show that Cdc42 overexpression reduced TN aggressive phenotype through the methylation of ID4 (inhibitor of Differentiation) promoter. Briefly, MDA-MB321 cell lines were transfected with a Cdc42-GFP vector and afterwards ID4 methylation status was measured by droplet digital and conventional Methyl Specific PCR. MS-MLPA assay revealed that ID4 methylation increased significantly in the Cdc42 transfected cells and interestingly, the methylation val-