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REUNIÓN DE SOCIEDADES DE BIOCIENCIAS 2021

**LXVI REUNIÓN ANUAL DE LA
SOCIEDAD ARGENTINA DE INVESTIGACIÓN CLÍNICA (SAIC)**

**LXIX REUNIÓN ANUAL DE LA
SOCIEDAD ARGENTINA DE INMUNOLOGÍA (SAI)**

**LIII REUNIÓN ANUAL DE LA
ASOCIACIÓN ARGENTINA DE FARMACOLOGÍA EXPERIMENTAL (AAFE)**

**XI REUNIÓN ANUAL DE LA
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EDITORES RESPONSABLES
Dr. Alejandro Curino
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Carrillo MC[1,2]
[1]Área Morfología, Facultad de Ciencias Bioquímicas y Far-macéuticas, Universidad Nacional de Rosario y CONICET
[2]Instituto de Fisiología Experimental (IFISE), CONICET

Our group has postulated supplementation with δ-tocotrienol (E) to interferon alpha (IFN) therapy as a strategy to treat liver cancer be-cause the combined treatment inhibits cell growth and metastatic properties and increases apoptosis in hepatocarcinoma cells.

In this work we studied the effects of the combination of IFN and E on normal angiogenesis, using EA.hy926 human umbilical vein endothelial cells.

Our hypothesis is that E supplementation to IFN therapy has signif-icant advantages in the angiogenesis process compared to individ-ual IFN treatment.

We treated EA.hy926 cells with 10000 U/I IFN (IFN-group), 12,5 uME (E-group), the combination of both drugs (IFN-E-group) or ve-hicles (C-group). We performed the MTT assay to determine cell via-bility at 72 h, constructing the dose-response curves to calculate the IC50 values. Combination index was also calculated (Compusyn). Besides, we performed the wound healing assay to determine mi-gration at 6 h and invasion assays in transwell chambers at 24 h. The results were tested by one-way ANOVA, followed by Tukey's test (3 independent experiments; n=4 in each one). As expected, IFN-E-group showed a higher decrease in cell viability (-63%*#) compared to monodrug therapy: IFN-group (-22%*), E-group (-21%*). Combi-nation index showed synergism between IFN and E. In the migration assay, IFN-E-group did not show a significant decrease (-16 %*) compared to monodrug therapy: IFN-group (-16%*) and E-group (-14%*). Finally, IFN-E-group showed a significant diminution in the invasion assay(-96 %* #) compared to monodrug therapy: IFN-group (-33%*) and E-group (-87%*). * p<0.05 vs C-group; #p<0.05 vs monotherapies. In summary, we demonstrate that addition of E to IFN therapy reduces proliferation, migration and invasion of human EA.hy926 endothelial cells, processes that are necessary for normal angiogenesis. In this regard, combined treatment might open a po-tential clinical target against angiogenesis in the future.

436. (053) **GEF-H1 DRIVES TUMOR FORMATION AND METAS-TASIS IN BREAST CANCER CELLS**

Lucía Fernández Chávez, Exequiel Gonzalo Alonso, Karen Schweitzer, María Julia Ferronato, Marilina Mascaró, María Marta Facchinetti, Alejandro Carlos Curino and Georgina Pa-mela Coló.
Laboratorio de Biología del Cáncer, Instituto de Investiga-ciones Bioquímicas de Bahía Blanca (INIBIBB-UNS- CONI-CET), Argentina.

RhoGTPases family is involved in several biological process includ-ing gene transcription, cell polarity, migration and invasion. RhoGT-Pases switch between on and off states and are regulated by sever-al GEFs (activators) and GAPs/RhoGDIs (inactivators).

The aim of this work is to study the role of a particular RhoA-GEF, GEF-H1, in breast cancer (BC) progression. We observed by im-munostaining a significant increase in GEF-H1 protein expression in BC human biopsies compared with non-tumoral tissue (n=76, p=0.0287). In addition, GEF-H1 expression correlated with the inva-sive potential of human and murine BC cell lines. To further study the role of GEF-H1 in tumor development, we generated GEF-H1- knock out (KO) BC cells using CRISPR/Cas9 technology. A decrease in proliferation, migration, invasion and anchorage-independent colony formation rates was observed in GEF-H1-KO cells compared to wild type (WT) cells (p<0.001). These results correlated with reduced focal adhesion formation and its downstream signalling. Further-more, BALB/c mice were subcutaneously inoculated with GEF-H1 KO cells, showing a significant delay in tumor formation (p<0.01) and lung metastasis development compared with mice inoculated with WT cells.

These results demonstrate that GEF-H1-RhoA activation mediates the signalling pathways involved in controlling cell proliferation, mi-gration and invasion of BC cells. In vivo assays and human biopsies studies suggest that GEF-H1 expression in BC cells might indeed contribute to tumor progression.

437. (057) **ANTICANCER ACTIVITY OF NOVEL COPPER(II) COMPLEX WITH A SCHIFF-BASE LIGAND ON IN VITRO AND IN VIVO OSTEOSARCOMA CANCER MODELS**

Lucia M. Balsa [1], Luisina M Solernó [2], Maria R. Rodriguez [1], Beatriz Parajón-Costa [1], Ana M. Gonzalez-Baró [1], Natasha T. Sobol [2], Daniel F. Alonso [2], Juan Garona [2,3], Ignacio E. León [1]
[1] CEQUINOR (CONICET-CCT La Plata-UNLP), Bvd. 120 N°1465, B1900AVV La Plata, Argentina; [2] Centro de Onco-logía Molecular y Traslacional (COMTra), Universidad Nacio-nal de Quilmes; [3] Centro de Medicina Traslacional (Unidad 6), Hospital de Alta Complejidad en Red El Cruce "Dr. Néstor Carlos Kirchner" S.A.M.I.C.

Osteosarcoma (OS) is the most common bone malignant tumor, affecting mainly children and young adults. Cisplatin has been effective for the treatment of different solid tumors, including OS. However, cisplatin treatment often results in the development of chemoresistance and several side effects, leading to therapeutic failure. In this sense, copper compounds have shown to be poten-tially effective as antitumor agents, attracting increasing interest as alternatives to usually employed platinum derived drugs.

The aim of this work is to evaluate the *in vitro* and *in vivo* antitumor-al activity against MG-63 cells of the nitrate salt of a novel Cu(II) cationic complex containing a tridentate hydrazone ligand, Cu(HL) for short.

Cytotoxic activity on MG-63 cell line was evaluated in 2D (mono-layer) and 3D (spheroids) models. Cu(HL) significantly reduced cell viability after 24 h treatment in both models (IC_{50} 2D: 1.98 ± 0.51 μM; 3D: 9.05 ± 1.0 μM) (p<0.001). Further studies demonstrated that Cu(HL) inhibits cell proliferation and conveys cells to apoptosis, determined by flow cytometry. Cu(HL) showed a great genotoxicity, evaluated by comet assay.

Finally, we assessed *in vivo* anticancer activity in animals bearing growing OS s.c. xenografts. Treatment during 4 weeks with Cu(HL) (2 mg/kg i.p. three times per week) markedly impaired tumor pro-gression, enhancing necrosis and reducing tumor growth rate and mitotic index (p<0.01). Treatment with an equivalent low dose of reference metallodrug cisplatin (2 mg/kg i.p. three times per week) failed to inhibit tumor growth.

Taken together, these results show that Cu(HL) has a promising an-ticancer activity against *in vitro* and *in vivo* OS models.

438. (058) **IMPACT OF IDH MUTATIONS ON THE IMMUNOLOG-ICAL LANDSCAPE OF GLIOMAS: A TCGA META-ANAL-YSIS BASED ON THE 2021 WHO CLASSIFICATION OF BRAIN TUMOURS**

Nazareno Gonzalez[1], Antonela S. Asad[1], José Gómez Esca-lante[2], Jorge A. Peña Agudelo[1], Alejandro J. Nicola Candia[1], Matías García Fallit[1,3], Adriana Seilicovich[1,4], Marianela Can-dolfi[1]
1. Instituto de Investigaciones Biomédicas (INBIOMED, UBA-CONICET), Facultad de Medicina, Universidad de Bue-nos Aires, Argentina, 2. Instituto de Oncología Ángel H. Ro-ffo, Buenos Aires, Argentina, 3. Departamento de Química Biológica, Facultad de Ciencias Exactas y Naturales, Univer-sidad de Buenos Aires, Argentina, 4. Departamento de Biolo-gía Celular e Histología, Facultad de Medicina, Universidad de Buenos Aires, Argentina.

Mutations in the enzyme isocitrate dehydrogenase genes (mIDH) are currently used to classify diffuse gliomas, the most common ma-lignant primary brain tumours in adults. Additional genetic lesions led to the most recent WHO classification that allows stratification in four tumor entities, mIDH gliomas [Oligodendrogliomas (OD) and Astrocytomas (AA)], and wtIDH gliomas: [Glioblastoma (GBM)-like and GBM]. While mIDH clearly correlates with better prognosis, the role of this mutation in antitumor immunity remains controversial. First, we predicted the level of infiltrating immune and stroma cells by ESTIMATE scores and both were significantly lower in mIDH patients. We also found reduced expression of immunoregulatory genes (PD-LI, PD-1, CTLA-4, IDO1, IL-10, LAG3 and TIM3) in mIDH biopsies (p<0.05, vs. wtIDH). Moreover, PD-L1 exhibited a strong