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Our group has postulated supplementation with δ -tocotrienol (E) to interferon alpha (IFN) therapy as a strategy to treat liver cancer because 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 significant advantages in the angiogenesis process compared to individual IFN treatment.

We treated EA.hy926 cells with 10000 U/I IFN (IFN-group), 12,5 μ M (E-group), the combination of both drugs (IFN-E-group) or vehicles (C-group). We performed the MTT assay to determine cell viability 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 migration 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%*). Combination 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 potential clinical target against angiogenesis in the future.

436. (053) GEF-H1 DRIVES TUMOR FORMATION AND METASTASIS 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 Pamela Coló.

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RhoGTPases family is involved in several biological process including gene transcription, cell polarity, migration and invasion. RhoGTPases switch between on and off states and are regulated by several 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 immunostaining 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 invasive 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. Furthermore, 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, migration 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

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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 potentially 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 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 (monolayer) and 3D (spheroids) models. Cu(HL) significantly reduced cell viability after 24 h treatment in both models (IC₅₀ 2D: 1.98 \pm 0.51 μ M; 3D: 9.05 \pm 1.0 μ M) (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 progression, enhancing necrosis and reducing tumor growth rate and mitotic index (p<0.01). Treatment with an equivalent low dose of reference metaldrug 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 anticancer activity against *in vitro* and *in vivo* OS models.

438. (058) IMPACT OF IDH MUTATIONS ON THE IMMUNOLOGICAL LANDSCAPE OF GLIOMAS: A TCGA META-ANALYSIS BASED ON THE 2021 WHO CLASSIFICATION OF BRAIN TUMOURS

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Mutations in the enzyme isocitrate dehydrogenase genes (mIDH) are currently used to classify diffuse gliomas, the most common malignant 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-L1, PD-1, CTLA-4, IDO1, IL-10, LAG3 and TIM3) in mIDH biopsies (p<0.05, vs. wtIDH). Moreover, PD-L1 exhibited a strong