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REUNIÓN CONJUNTA SAIC SAI&FAIC SAFIS 2022

LXVII REUNIÓN ANUAL DE LA SOCIEDAD ARGENTINA DE INVESTIGACIÓN CLÍNICA (SAIC)

LXX REUNIÓN ANUAL DE LA SOCIEDAD ARGENTINA DE INMUNOLOGÍA (SAI) & 3ER CONGRESO FRANCO-ARGENTINO DE INMUNOLOGÍA (FAIC)

REUNIÓN ANUAL 2022 DE LA SOCIEDAD ARGENTINA DE FISIOLOGÍA (SAFIS)

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Hotel 13 de Julio – Mar del Plata

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that Caco2-FABP1as cells have decreased *de novo* FA synthesis ($p<0.05$), linking this protein with the modulation of endogenous FA metabolism as well. Consistently, FABP1 *knockdown* reduced the level of enzymes related to FA synthesis, suggesting that FABP1 may affect lipid metabolism through the regulation of gene expression. To gain further insights into this aspect, we performed RNA-Seq in Caco2-FABP1as cells and mock transfected control cells. We identified profound changes in Caco-2 cells transcriptome following FABP1 *knockdown* that have not previously reported, setting the stage for an in-depth investigation of FABP1-mediated lipid metabolism rewiring. Although preliminary, our results suggest that FABP1 represents a key transcriptional and metabolic regulator in CRC cells.

611. (435) **ANALYSIS OF RAC1 EXPRESSION IN COLORECTAL CANCER CLINICAL SAMPLES ACCORDING TO MSI/MSS STATUS AND IN VITRO SENSITIVITY OF MSS CELL LINES TO 1A116 RAC1 INHIBITOR**

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Rac1 GTPase has a critical role in the progression of colorectal cancer (CRC), regulating processes related to growth, chemoresistance and immunomodulation. Despite the fact that immune checkpoint inhibitor-based immunotherapy has revolutionized CRC management, only a small subgroup of patients bearing tumors with microsatellite instability (MSI) benefit from this approach. The aim of the present work was to first study RAC1 target expression in microsatellite stable (MSS) or MSI CRC samples using bioinformatics, and second to explore the antitumoral effects of 1A116, a selective RAC1 inhibitor previously developed by our research group, on different murine and human MSS CRC cells. We used the TCGA database and the Gene Expression Profiling Interactive Analysis II (GEPIA2) platform in order to assess differential expression of RAC1 in normal adjacent and CRC tissue, and then evaluate target expression according to MSS, MSI-low and MSI-high tumor status. After confirming that the target of interest is upregulated in CRC versus normal tissue, we observed that RAC1 expression is significantly higher in MSI-low and especially MSS CRC, than in MSI-high tumor implying RAC1 as a possible therapeutic target in patients MSS/MSI-low tumors. In vitro, 1A116 (5-50 μM) impaired tumor cell growth on highly aggressive murine CT-26 and human HT-29 MSS CRC cells. Furthermore, cytostatic activity of the compound was assessed on 3D spheroid growth using the hanging drop method. After long-term exposure to 10 and 25 μM concentrations of 1A116 a significant arrest of CRC spheroid growth was obtained in both treatments. In addition, after exploring 1A116 impact on expression/secretion of cytokines, we observed that the compound seems to modulate key immune and inflammatory mediators. These results lay the groundwork for further preclinical exploration of 1A116 RAC1 inhibitor as a potential therapeutic tool to increase response to immunotherapies in aggressive and refractory MSS CRC.

612. (492) **CHARACTERIZATION OF ADRB2-MEDIATED ANTITUMORAL EFFECTS AND MECHANISMS OF ACTION OF β-BLOCKER PROPRANOLOL IN OSTEOSARCOMA**

Solernó, Luisina M.[1-2]; Sobol, Natasha T.[1-2]; Ferrero, Maximiliano R.[4]; Llavona, Candela[1-2] Capobianco, Carla S.[1]; Bruzzone, Ariana[5]; Gottardo, M. Florencia[1-2]; Garona, Juan[1-2-3].

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Osteosarcoma (OSA) is still associated with limited response to standard-of-care therapy and alarmingly elevated mortality rates. Our group recently reported for the first time that PPN, a repurposed β1/2-adrenergic receptor (ADRB1/2) antagonist, was capable of reducing tumor-associated angiogenesis and xenograft aggressiveness using different OSA preclinical models. The objective of this work was to characterize PPN ADRB2-mediated effects and mechanisms of action on OSA growth, migration and response to chemotherapy. After confirming ADRB2 expression by RT-qPCR in MG-63 and U-2OS OSA cells, pro-mitogenic effects of ADRB agonists epinephrine and norepinephrine were associated with downstream activation of MAPK-associated signaling pathways, as evaluated by western blotting. ADRB2 knockdown by transfection with ADRB2-targeting siRNA reduced in vitro aggressiveness of OSA cells and impaired PPN cytostatic activity, confirming target specificity of the drug. As evaluated by flow cytometry, a significant arrest in the G_0/G_1 cell cycle phase of MG-63 and U-2OS cells was observed after 24 h treatment with PPN (50 μM), which was associated with a significant reduction in CCND1 gene expression, a key cell cycle regulator. OSA growth inhibition was not associated with apoptosis induction. β-blockade with PPN inhibited OSA cell chemotaxis, vasculogenic mimicry and capillary-like tube formation on Matrigel® coated substrates. Migration inhibition was linked to blockade of EGF-induced actin reorganization and stress fiber formation. After histological analysis, *in vivo* therapeutic benefits after addition of PPN (10 mg/kg i.p.) to cisplatin-based metronomic chemotherapy (2 mg/kg i.p.) correlated with reduced tumor mitotic index and increased necrosis. All results were significant at $p<0.05$ (t test or ANOVA, GraphPad Prism). We propose PPN as a potential cost-effective co-adjuvant therapy for OSA management. Further translational studies on metastatic disease are in progress.

613. (493) **IMPACT OF DESMOPRESSIN TREATMENT ON LYMPHOCYTE INFILTRATION AND LUNG PRE-METASTATIC NICHE FORMATION BY COLORECTAL CANCER CELLS**

Natasha Tatiana Sobol[1;2;3], Luisina María Solernó[1;2;3], Candela Llavona[1;3], María Florencia Gottardo[1;2;3], Valeria Inés Segatori[1;2;3], Daniel Fernando Alonso[1;2;3], Juan Garona[1;2;3]

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Metastatic colorectal cancer (mCRC) still stands as a therapeutic challenge in which tumor cell spread to liver and lungs accounts for most of CRC-related mortality. Desmopressin (dDAVP) is a synthetic vasopressin analog and repurposed hemostatic drug in oncology, with reported antimetastatic and angiostatic action in aggressive tumors. Given that the metastatic niche and stroma-tumor cell interactions are crucial steps during the establishment of metastases, our aim was to explore the impact of dDAVP treatment on the pre-metastatic niche formation and the modulation of lymphocyte infiltration in the lung, the second most common site of metastasis in CRC. Firstly, we characterized the kinetics (7, 15 and 21 days) of lung metastases development in syngeneic Balb/c mice after i.v. inoculation of CT-26 CRC cells, confirming massive tissue colonization and more than 30 macronodules/lung (>1mm) at day 21. Furthermore, to asses the impact of CRC cell-secreted factors on the establishment and growth of metastatic cells we injected CT-26 conditioned medium in Balb/c mice prior to tumor cell inoculation for 4 consecutive days, which led to a 3-fold increase in the number of lung metastasis. Interestingly, this phenomenon was completely reverted after dDAVP co-administration at clinically relevant doses (1 μg/kg i.v.). We then studied the impact of dDAVP on the recruitment of inflammatory cells to the lung during the early steps of metastatic colonization in immunocompetent mice by flow cytometry, where i.v. treatment with the peptide significantly increased by 3 times the CD8+ cell population infiltrating the tissue. No significant changes were observed in the CD4+ population nor in the circulating CD4+ or CD8+T