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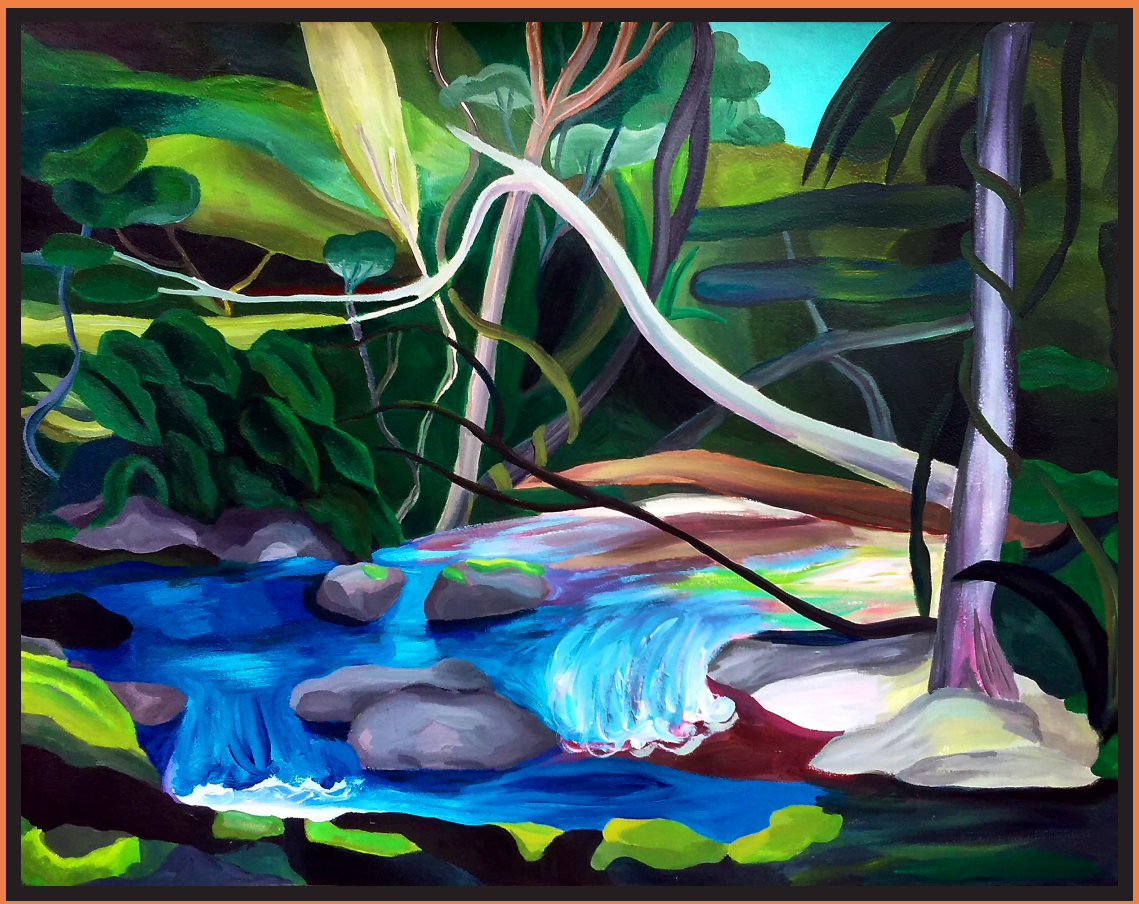

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15-17 de noviembre de 2023
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(p<0.01), indicating a more plastic phenotype. We also performed an RNA-seq analysis on tumor-derived stem cell-enriched spheroids obtained from independent patient samples. We found that KANSL2-knock down cells led to the upregulation of genes associated with epithelial-mesenchymal-like transition (p<0.001) and Hippo signaling pathway transcriptional targets (p<0.001), both processes linked to increased tumor aggressiveness. Importantly, these data were further validated using the "subtype me" GBM subtype classification tool, confirming KANSL2 decrease induces a transition to a mesenchymal subtype. Functional experiments in U251 and U87 GBM cell lines showed increased migratory capacity, elevated VEGF protein expression, and enhanced neovascularization in vivo of KANSL2 knock-down cells. Based on these findings, we propose KANSL2 has a role as a modulator of plasticity and aggressiveness in GBM, which is intricately affected by cellular subtype and migratory capacity. Additionally, KANSL2-RFP tagged overexpression in U87 cells led to a decrease in protein levels of intracellular YAP1, suggesting an inverse regulation of KANSL2 and the Hippo signaling pathway as regulators of different identities of plastic tumors.

311. 120. **METABOLIC EFFECTS OF T47D CELLS IN MAMMARY ADIPOSE TISSUE**

Francisco Damián Rosa[1], Ignacio Aiello[2], María Cecilia Lira[1], Iara Castellanos[1], Alejandra Graciela Palma[1], Juliana Lourdes Bernacchia[1], Natalia Paladino[2], Mónica Alejandra Costas[1], María Fernanda Rubio[1].

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In previous work we have observed that TNF is able to induce lipolysis in adipose tissue (AT) explants from mammary glands of C57-BL/6J mice and that the breast cancer cell line T47D secretes high levels of TNF. The aim of this work was to analyze the metabolic changes in AT produced by factors secreted for T47D cells. Wild type (wt) or TNF receptor 1 knock out (KO) AT explants were stimulated for 5 days with T47D cell line conditioned media (CM). The number of adipocytes per unit area of paraffin-embedded histological sections was measured to assess adipocyte size. The T47D CM induced a decreased in adipocyte size (1.8 ± 0.06 respect to wt basal, p<0.05). In addition, tissue total lipid content was studied by gravimetry, after Bligh & Dyer extraction and AT glycerol secretion by colorimetric assay. Stimulation with T47D CM decreased total lipid content (0.55 ± 0.04 respect to wt basal, p<0.05) and increased glycerol secretion (2.69 mg/l ± 0.92 wt T47D vs 0.42 mg/l ± 0.16 wt basal, p<0.05). To assess whether these lipolytic effects of T47D CM could be mediated by TNF, we performed these experiments in the KO AT model. T47D CM had no significant differences in total tissue lipid content respect to KO basal (1.05 ± 0.15 KO T47D; 0.98 ± 0.04 KO basal respect to wt basal; p<0.05). Although, T47D CM increased adipocyte size respect to KO basal (1.4 ± 0.1 KO T47D; 2.8 ± 0.1 KO basal respect to wt basal; p<0.05). Interesting, adipocytes in the KO AT were smaller than in the wt model (2.8 ± 0.1 KO basal respect to wt basal; p<0.05). Also, treatment with T47D CM increased glycerol secretion respect to KO basal (4.46 mg/l ± 0.42 KO T47D vs 0.44 ± 0.09 KO basal; p<0.05). In conclusion, we have observed that T47D stimulation induces a lipolytic profile in adipose tissue and, although TNF may be a lipolytic signal in the T47D CM, our results indicate that there are other factors that could also mediate these changes in AT lipid metabolism.

312. 145. **INCREASED EXPRESSION OF GEF-H1 IN THYORID CANCER PROMOTES CELL PROLIFERATION, MIGRATION AND INVASION**

Lucía Fernández Chávez[1], Vicente Bermúdez[1], Valentina Arenal[1], Exequiel Gonzalo Alonso[1], Karen Schweitzer[1], Pamela Pichel[3], Sergio Recio[3], María Julia Ferronato[1], María Eugenia Fermento[1], Eliana Noelia Alonso[1], Mateo Nicolás Campos Haedo[2], Cinthia Rosemblit[2], María Marta Facchinetti[1], Alejandro Carlos Curino[1] y Georgina Pamela Coló[1].

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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). We identified a GEF-H1 as one of the main activators of RhoA. In addition, we have observed that GEF-H1 is involved in cell proliferation, cytoskeleton remodelling, cell migration and invasion, as well as in breast tumor development and metastasis. Rho GTPases contribute to tumor initiation and progression, however, the role of RhoA activators has not yet been study in thyroid cancer (TC). Hence, the aim of this work is to study the role of GEF-H1 in TC development. TC is the most prevalent endocrine neoplasia and the main cause of death is the metastasis. By bioinformatics analysis we found GEF-H1 mRNA and protein overexpressed in tumoral thyroid tissue (TT) compared with non-tumoral tissue (NT). In addition, the expression of GEF-H1 was significantly higher in papillary and anaplastic thyroid carcinomas than in NT (p<0.05) and increased in papillary carcinomas with lymph node invasion and/or metastasis (p<0.0001). We observed by immunostaining a significant increase in GEF-H1 protein expression in TC human biopsies compared with NT (n=89, p<0.0001). In addition, we observed by immunofluorescence staining high GEF-H1 protein expression in thyroid primary carcinoma cell culture compared with normal thyroid cells. To further study the role of GEF-H1 in tumor development, we generated GEF-H1-knock out (KO) cells using CRISPR/Cas9 technology from a thyroid papillary carcinoma cell line (TPC-1). A decrease in proliferation, migration and invasion rates was observed in GEF-H1-KO cells compared to wild type cells. Our results suggest that GEF-H1 could be used as a potential tumor biomarker and/or therapeutic target in TC, since it could be involved in controlling cell proliferation, migration, and invasion of TC cells.

313. 239. **THE DEVELOPMENT OF LUNG METASTASIS IN A MOUSE LUMINAL BREAST CANCER MODEL DEPENDS ON ITS PREVAILING PROGESTERONE RECEPTOR ISOFORM**

Leo Saldain[1], Andrés Elia[1], Gabriela Pataccini[1], Martin Abba[2], Claudia Lanari[1], Paola Rojas[1]

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We propose that luminal breast carcinomas with higher levels of the Progesterone Receptor isoform A (PRA) than the isoform B (PRB), named PRA-high (PRA-H), are those that are inhibited to grow by antiprogestins, whereas those with the opposite ratio (PRB-H) may be even stimulated with antiprogestin treatment. In previous studies, we suggested that PRB-H tumors are more proliferative and less metastatic than PRA-H tumors. To confirm our results, we decided to compare the growth and the number of lung metastatic foci using the C7-2-HI (PRA-H) murine mammary carcinoma and its antiprogestin resistant variant C7-2-HIR (PRB-H). Tumors were inoculated subcutaneously in BALB/c mice and then euthanized 42 and 90 days (n=3-5/group) later. Tumors and lungs were fixed, paraffin-embedded and stained with hematoxylin-eosin. A higher amount of foci were generated by the PRA-H tumor compared to the PRB-H counterpart (Mann-Whitney, 42 days: p=0.086; 90 days p=0.037), regardless of the fact that the growth rate of the former was almost 2 times lower compared with the latter (linear regression, p<0.01). At day 42, the metastatic foci generated by the PRA-H tumor tended to be larger than those generated by the PRB-H. However, after 90 days we observed that the few foci generated by the PRB-H tumors were larger than those generated by the PRA-H tumors. A higher degree of differentiation was observed in the metastatic foci that was independent of the tumors' PR isoform ratio. We also performed an RNA-Seq analysis of both tumors, which showed upregulation in motility and migration genes and a downregulation in the G2 phase genes (e.g.) in the C7-2-HI tumor (log fold change (LFC) > 1 and FDR < 0.05) compared to the PRB-H variant, in agreement with our