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REUNIÓN CONJUNTA DE SOCIEDADES DE BIOCIENCIAS

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JOINT MEETING OF BIOSCIENCE SOCIETIES

LXII ANNUAL MEETING OF ARGENTINE SOCIETY OF CLINICAL INVESTIGATION (SAIC)

LIII ANNUAL MEETING OF ARGENTINE SOCIETY OF BIOCHEMISTRY AND MOLECULAR BIOLOGY (SAIB)

LXV ANNUAL MEETING OF ARGENTINE SOCIETY OF IMMUNOLOGY (SAI)

MEETING OF ARGENTINE SOCIETY OF ANDROLOGY (SAA)

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LA TAPA

María Esther Gené, **Imagen ígnea**, 1996.

Acrílico sobre tela, 110 x 95 cm. Cortesía de la Comisión Nacional de Energía Atómica, Predio TANDAR, Centro Atómico Constituyentes. Presidente de la Comisión Organizadora de la Exposición Permanente: Dr. A.J.G.Maroto.

María Esther Gené nació en Buenos Aires. Cursó Historia del Arte y Estética con Blanca Pastor y Nelly Perazo. Se inició en el taller de Centa Bertier y continuó su formación con Miguel Dávila. Participó del grupo de investigación plástica que dirigió Emilio Renart. Integró el Grupo Gen y formó el Grupo Fusión. Realizó numerosas exposiciones colectivas e individuales (Museos Municipal de Bellas Artes de Luján, Fernán Félix de Amador, de Arte Moderno de la Ciudad de Buenos Aires, Fundaciones San Telmo y Banco Mayo, Fundación Andreani, Patio Bullrich, Galería Kristel K., Salón ICCED de Pintura, entre otros). Sus obras se encuentran en colecciones privadas de Argentina, México, Alemania, España, Uruguay y EE.UU.

[1] Comisión Nacional de Energía Atómica. Artistas Plásticos con la CIENCIA, Centro Atómico Constituyentes, Predio TANDAR, Buenos Aires, 1999; En: *http://www2.cnea.gov.ar/xxi/artistas/artistasplasticos.htm*

Our laboratory described that Smaug1/2, a translational repressor that binds specific motifs termed *Smaug recognition elements* (SREs), forms cytoplasmic silencing bodies similar to Processing Bodies. Rodent Smaug1/Samd4a modulates synaptic plasticity (Baez et al., J Cell Biol 2011) and other authors reported that Smaug2/Samd4b directs early neuronal differentiation (Amadei et al., J Neurosci 2015). In addition, Smaug1/Samd4a KO mouse show strong developmental defects of mesenquimal tissues (bone, cartilage, muscle and fat). Our objective is to investigate how Smaug1 / 2 regulate mesenquimal differentiation. We used mesenquimal cell lines and specific antibodies and found that Smaug proteins forms mRNA silencing bodies, which are different from PBs. Strickingly, Smaug silencing inhibits cell differentiation. We designed an algorithm to predict SREs and found several potential targets relevant to this phenotype that are conserved in mouse and human. Quantitative PCR indicated that Smaug KD prevents the up-regulation of key transcription factors that govern cell differentiation ($p<0,05$). In particular, western blot analysis indicates that the early pro-developmental transcription factor C/EBP-β are downregulated upon Smaug KD. We are currently analyzing the contribution of Smaug1 and Smaug2 and which specific targets are under their respective control.

Keyword: SMAUG2, mesenquimal differentiation

(331) **A TANKYRASE INHIBITOR IMPAIRS TUMOUR GROWTH AND ANGIOGENESIS THROUGH THE WNT/β-CATENIN PATHWAY ATTENUATION**

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Aberrant regulation of Wnt signaling pathway is a prevalent theme in cancer biology. While it has been demonstrated to be involved in many types of tumours it has been poorly studied in ovarian cancer. We analyzed the effect of inhibiting Wnt/β-catenin in a xenograft model of human ovarian cancer. A human ovarian adenocarcinoma cell line (IGROV-1) was subcutaneously injected in 6-8 weeks-old female nude mice. Once the tumour was palpable, we injected a tankyrase inhibitor, which attenuates Wnt/β-catenin signalling (XAV939: 2.5 and 5 mg/kg) every two days three times. Mice were euthanized 3 days after the last injection. The involvement of Wnt/β-catenin pathway in tumour growth, morphology and angiogenesis was evaluated.

Our results showed a significant decrease in tumour size when mice were treated with XAV939, which strikingly, was higher at the 2.5 mg/kg dose than the 5 mg/kg dose (day 7: no treated animals vs. 2.5 mg/kg group, $p<0.001$; no treated animals vs. 5 mg/kg group: $p< 0.05$). No significant differences were appreciated in mice weight between groups. There was also a significant decrease in β-Catenin and Cyclin D1 levels measured by western blot at both doses used. On the other hand, we observed a decrease in the endothelial cell area stained with CD31 marker. Additionally, we detected a decrease in the periendothelial cell area, measured using α-Smooth-muscle-actin, compared with tumours from animals with no treatment. In hematoxilin-eosin stained sections of tumours we distinguished that the morphology notably changed after treatment with XAV939. A tumour loss of integrity and accumulation of interstitial fluid was evident and dose dependent.

In conclusion, we demonstrate a clear involvement of Wnt/β-catenin in ovarian tumour growth and we suggest and implication of this pathway in tumour angiogenesis.

Keywords: Wnt signaling, ovarian cancer, angiogenesis, tumour growth

(1634) **WNT5A REGULATES N-CADHERIN SHEDDING IN MELANOMA**

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The loss of E-cadherin and the gain of N-cadherin expression, usually known as “cadherin switching” is a crucial process in melanoma progression. The loss of E-cadherin expression has been correlated with advanced melanoma stages and poor prognosis, whereas the upregulation of N-cadherin associates with increased cell motility and metastasis. N-cadherin function is also regulated by shedding by cellular proteases that cleave the 135 KDa full-length protein (p135) in its N-Terminal Fragment of 95 KDa (ectodomain or p95) and the C-Terminal Fragment (CTF, 40 KDa).

Wnt5a is responsible for the activation of several Wnt-no canonical signals that have been implicated in tumor progression. In a previous work we demonstrated that Wnt5a induces cell motility and migration by inducing the expression of N-cadherin in melanoma. In the present work we studied the regulation of N-cadherin shedding by Wnt5a. Treatment of three melanoma cell lines (A375, Lu1205 and Mewo) with Wnt5a conditioned media significantly increased the amount of cellular p95 and the ratio p95/p135 ($p <0.05$). In line with these results, silencing Wnt5a expression in WM9 cells (a cell line with high Wnt5a expression) reduced N-cadherin shedding ($p <0.05$). The cleavage of N-cadherin was further confirmed by detecting the release of the ectodomain to the culture media and the release of the CTF to the cytosol.

N-cadherin shedding induced by Wnt5a was reduced to different extent in different cell lines by the pharmacological inhibitors LY294002 and Go6976, suggesting the participation of Akt and PKC pathways, respectively. In line with these data, P-Akt levels were increased ($p <0.05$) or reduced ($p <0.05$) upon Wnt5a treatment and Wnt5a silencing, respectively. In agreement Treatment of cells with TPA or Ionomycin induced N-cadherin shedding confirming the participation of PKC in this process. In summary, our results indicate that Wnt5a regulates N-cadherin shedding via PI3K/Akt and PKC pathways.

Keywords: Melanoma, N-Cadherin, Shedding, Wnt5a

(1400) **COMPARATIVE METASTATIC AND NONMETASTATIC TUMOR RESPONSE TO HYALURONIC ACID TREATMENT. ROLE OF BETA-CATENIN AS A POSSIBLE MEDIATOR**

Sofía Aylén Valla, Gianina Demarchi, Daiana Vitale, Daiana Del Dago, Carolina Cristina, Laura Alaniz
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Tumor microenvironment has a significant role in tumor malignancy, modulating several functions as angiogenesis. In this work we studied the relation of the extracellular matrix component, Hyaluronic acid(HA) and the protumoral signaling pathway Beta-Catenin and the effect of that interaction in angiogenic processes in tumors of different behavior. We used the metastatic breast cancer MDA-MB-231 cells and the nonmetastatic prolactinoma MMQ cells. Cells were treated with HA (20 mg/ml) or the Wnt synthesis inhibitor, IWP-2 (5uM) for 48hs. Protein levels were analyzed by WB or FC and VEGF biosynthesis measured by ELISA. We found that the HA-receptor CD44 has low expression in MMQ cells (3%) while it was high in MDA cells (98%). HA induced Beta-Catenin expression in MDA cells ($p<0,05$; N=3) and produced a trend of increase of the protein in MMQ cells. HA treatment was unable to modulate VEGF release in any of the cell lines (ns; N=3), although MDA supernatants of HA treated cells increased HMEC endothelial cell migratory capacity evaluated by wound healing assay ($p<0,001$; N=3). In order to determine whether Wnt/Beta-Catenin pathway affected tumor angiogenesis, we treated both cell lines with IWP-2 and observed a trend of reduction of Beta-Catenin levels and of increase of pGSK3 active form in MMQ cells; however, no effect was found in MDA cells (ns; N=3) suggesting that Beta-Catenin expression under HA treatment could be independent of Wnt ligands. Regarding VEGF secretion, IWP-2 reduced VEGF levels ($p<0,05$; N=3) in MMQ cells but not in MDA (ns; N=2). In accordance, IWP-2 treated MMQ supernatants showed a trend of reduction of HMEC cell migration. Our results suggest that the influence of HA on angiogenic responses could differ according to the aggressiveness of the tumor studied, which can be explained by a different sensitivity to HA in relation to CD44 expression and different mechanisms of regulation of Beta-Catenin.

Keywords: METASTASIS, ANGIOGENESIS, HYALURONIC ACID, BETA-CATENIN

(734) **AN AUTOCRINE WNT5A LOOP IS A MAIN MECHANISM OF CONSTITUTIVE NF-κB ACTIVATION IN MEL-**