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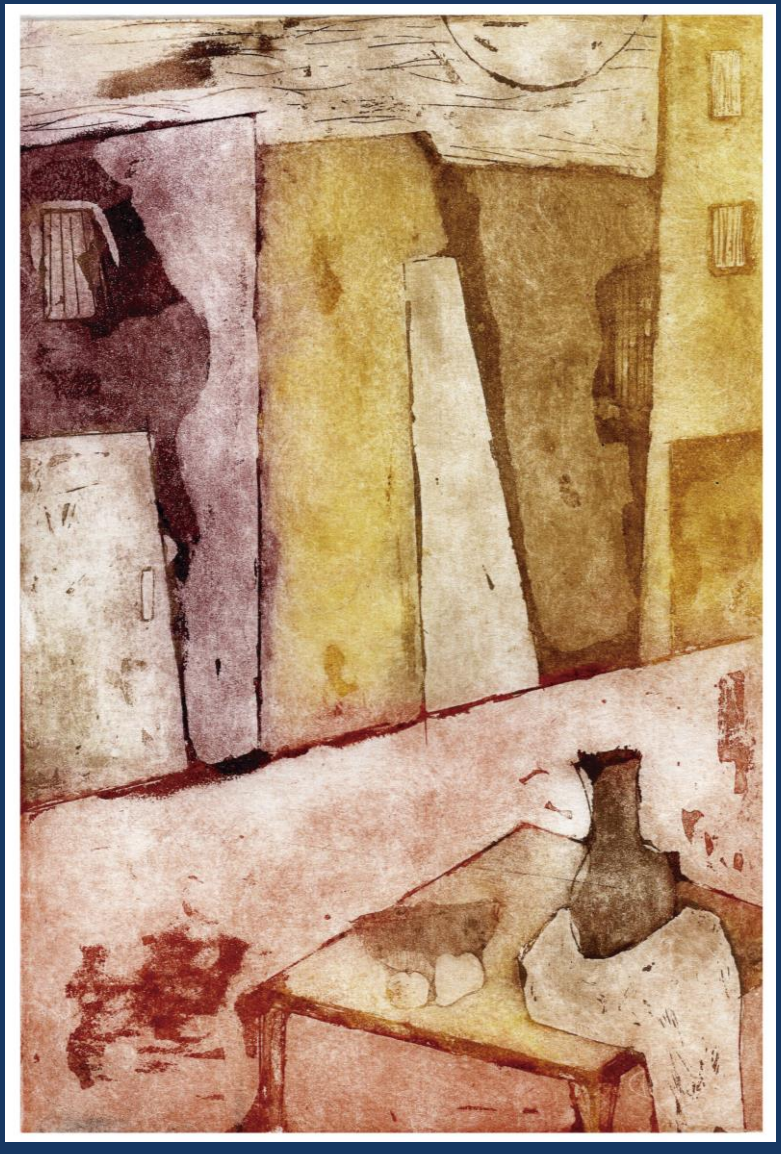

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La Tapa (Ver pág. 4)
Atardecer en la tarde
Antonella Ricagni

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REUNIÓN ANUAL DE SOCIEDADES DE BIOCIENCIA 2019

LXIV Reunión Anual de la
Sociedad Argentina de Investigación Clínica (SAIC)

LI Reunión Anual de la
Asociación Argentina de Farmacología Experimental (SAFE)

XXI Reunión Anual de la
Sociedad Argentina de Biología (SAB)

XXXI Reunión Anual de la
Sociedad Argentina de Protozoología (SAP)

IX Reunión Anual de la
Asociación Argentina de Nanomedicinas
(NANOMED-ar)

VI Reunión Científica Regional de la Asociación Argentina de Ciencia y Tecnología de Animales de Laboratorio (AACyTAL)

con la participación de
The Histochemical Society

13 - 16 de noviembre de 2019
Hotel 13 de Julio - Mar del Plata

EDITORES RESPONSABLES

Dra. Mónica Costas
Dra. Gabriela Marino
Dr. Pablo Azurmendi

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ANNUAL MEETING OF BIOSCIENCE SOCIETIES 2019

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The Histochemical Society

November 13th – 16th, 2019
Hotel 13 de Julio - Mar del Plata

CHIEF EDITORS

Dra. Mónica Costas
Dra. Gabriela Marino
Dr. Pablo Azurmendi

LA TAPA

Antonella Ricagni. **Atardecer en la calle**

Técnica: Aguatinta /aguafuerte. Año 2011. Medidas: 21 x 29 cm. Gentileza del autor.

Antonella Ricagni es Licenciada en Artes Visuales, con orientación en Grabado. Ha ejercido la docencia en Artes Plásticas en el nivel primario. Trabajó en varios museos como orientadora de sala y tallerista. Es escenógrafa egresada de la Escuela Metropolitana de Arte Dramático (EMAD). Ha realizado una residencia artística en México especializada en Xilografía.

Actualmente es docente en la materia Ilustración, en la carrera de Diseño Gráfico en la Facultad de Arquitectura, Diseño y Urbanismo, Universidad de Buenos Aires, y en Plástica y Tecnología en varias instituciones educativas en la ciudad de Buenos Aires.

Fuentes: https://www.behance.net/antoricagn37bb
https://www.linkedin.com/in/antonella-ricagni-4b48a0120/

QUÍMICA Y FISICOQUÍMICA BIOLÓGICAS (IQUIFIB), CONICET (2)

Abstract/Resumen: 4-methylumbelliferone (4MU) is a non-toxic coumarin derivative used as inhibitor of hyaluronan (HA) synthesis, but there are reports about independent effects of this inhibition. Currently, this drug is being studied on several neoplasms. Nevertheless, little is known about its effects on glioblastoma (GBM), the most frequent and malignant primary tumor of the central nervous system. HA is strongly involved in tumor progression, favoring cell proliferation and migration through its main receptors, CD44 and RHAMM, both associated with poor prognosis. GBM shows higher levels of HA than normal brain tissue. Given that current therapy for this tumor is ineffective and highly toxic, new drugs are needed for GBM treatment. Our hypothesis is that 4MU is a potential new drug for GBM therapy. Therefore, the aim of this work was to evaluate the effects of 4MU on cell proliferation, migration, senescence induction, expression of CD44 and RHAMM, and the receptors involved in HA-induced migration on LN229 and U251 human GBM cell lines. Cell proliferation was evaluated by BrdU incorporation assay, migration by the wound healing assay, senescence by SA-ß-gal assay and expression of receptors by Western blot (WB) and immunofluorescence (IF). We found that 4MU inhibited cell proliferation and migration in a dose-dependent manner in both cell lines ($p<0.05$). These effects were not prevented by the co-treatment with HA. Besides, 4MU increased the percentage of SA-ß-gal+ cells in a dose-dependent manner in U251 cell line, but in LN229 cells only at the higher dose ($p<0.05$). Furthermore, 4MU modulates the expression of RHAMM and CD44 ($p<0.05$). Regarding the implication of CD44 and RHAMM in HA-induced migration, we evaluated this process using blocking antibodies which prevented the effect of HA ($p<0.05$). In conclusion, we demonstrated that 4MU inhibited all studied processes involved in GBM malignancy, thus being a promising therapy for GBM.

0883 - IMIQUIMOD TREATMENT OF TRANSFORMED CELLS: NF-KB AND TLR-7/8 SIGNALLING INDEPENDENT DEATH.

Rodrigo ROCCO (1) | Sofia RABELLINI(1) | Adrián CAMBINDO BOTTO(2) | Manuel MUÑOZ(2) | Rosa WAINSTOK(1) | Adriana COCHÓN(3) | Silvina GAZZANIGA(3)

INSTITUTO DE QUÍMICA BIOLÓGICA DE LA FACULTAD DE CIENCIAS EXACTAS Y NATURALES (IQUIBICEN) (1); INSTITUTO DE FISIOLOGÍA, BIOLOGÍA MOLECULAR Y NEUROCIENCIAS (IFIBYNE)-UBA-CONICET (2); UNIVERSIDAD DE BUENOS AIRES-FACULTAD DE CIENCIAS EXACTAS Y NATURALES (3)

Abstract/Resumen: The immunotherapeutic agent imiquimod (IQ), an agonist of the Toll-like receptors (TLR) 7/8, has been reported to be effective in the treatment of several skin pathologies including melanoma and infantile haemangioma. In immune cells, the classic pathway for IQ signalling comprises TLR7 and NF-KB activation. Previously, we have demonstrated that IQ causes cell death, oxidative stress and loss of migratory ability in haemangioma and melanoma cells in vitro. In order to gain insight on IQ signalling mechanism in transformed cells, we studied TLR expression and the involvement of NF-kB in IQ-induced cell death. Murine melanoma B16F-1 and haemangioma H5V cells were treated with IQ (0, 5, 10 and 50 µg/mL) in the presence or absence of an NF-KB inhibitor (BAY 11-7082) during 24 hours. Cell viability was analysed by crystal violet staining and nuclear morphological changes were evaluated by a nuclear morphometric analysis (NMA) with ImageJ on Höescht 33258-stained nuclei. TLR-7/8 expression was assayed by RT-qPCR. Both H5V and B16F-1 cells suffered loss of viability (circa 50 %) at IQ 10 µg/mL but inhibition of NF-KB did not modify cell death levels. Likewise, NMA showed an increased number of small and regular nuclei (50-60 %, $p<0.05$) at IQ 10-50 µg/mL associated to apoptotic cells. The percentage was similar either with or without BAY 11-7082 treatment. In addition, after incubation with IQ+BAY, a slight tendency to the appearance of large regular nuclei, compatible with senescent cells, was detected in both cell lines accompanied by cytoplasmic vacuolization. With respect to TLR7 expression, low levels were obtained for H5V cells (0.13 ± 0.10) compared to ganglion and resulted undetectable for B16F1, as well as TLR8 expression in both cell lines. Consequently, these results suggest that IQ would be exerting its cytotoxic effect without involving NF-kB and TLR-7/8 signalling.

0893 - ASSESSMENT OF BACULOVIRAL VS ADENOVIRAL VECTORS FOR GENE DELIVERY IN EXPERIMENTAL BRAIN CANCER

Antonela Sofía ASAD (1) | Matías Luis PIDRE(2) | Sofía SAGRIPANTI(1) | Matías GARCÍA FALLIT(1) | Alejandro J. NICOLA CANDIA(1) | Camila Florencia ZUCCATO(1) | Mercedes IMSEN(1) | Víctor ROMANOWSKY(2) | Adriana SEILICOVICH(1) | Flavia ZANETTI(3) | Marianela CANDOLFI(1)

INBIOMED- INSTITUTO DE INVESTIGACIONES BIOMÉDICAS. UBA-CONICET (1); INSTITUTO DE BIOTECNOLOGÍA Y BIOLOGÍA MOLECULAR, FAC DE CS EXACTAS, UNIVERSIDAD NACIONAL DE LA PLATA (2); INSTITUTO DE CIENCIA Y TECNOLOGÍA "DR. CESAR MILSTEIN"; CONICET (3)

Abstract/Resumen: We aimed to compare the transduction efficiency and neuropathology of adenoviral (AdV) vs baculoviral (BV) vectors in order to develop therapeutic strategies for the treatment of brain cancer. Although AdVs can be produced in high titers and yield good transduction efficiency in the brain, the population exhibits pre-existing anti-AdV immunity, leading to transient transgene expression. BVs primarily infect insects at larval stage, but they also transduce cells from other species. Even though BVs are less stable than AdVs after long-term storage, their advantage is that pre-existing immunity against BVs has not been reported in humans. Our general hypothesis is that BVs may lead to more stable transgene expression than AdVs upon injection into naïve and neoplastic brain. We constructed AdV and BV encoding tdTomato under the control of the CMV promoter. Human and rat GB cell lines were incubated with different doses of AdV or BV for 48 h and transduction efficiency was assessed by microscopy. AdV (MOI 50-500) and BV (MOI 500-2000) transduced GB cell lines with similar efficiency. AdV ($\sim 10^7$ UFP) and BV ($\sim 10^6$ UFP) were injected by stereotactic surgery into orthotopic GL26 GB growing in the brain of C57Bl/6 mice and 5 d later, mice were perfused/fixed and brains were sectioned in cryostat. We detected comparable expression of tdTomato within tumors injected with either vector. AdV or BV were also injected into the striatum of naïve mice and 5 d later, brains were processed for immunohistochemistry to identify glial cells, showing that transduced brain cells were GFAP+. CD45 staining showed similar immune cell infiltration around BV and AdV injection sites and no signs of neurotoxicity were observed. Our findings indicate that both vectors transduce GB and glial cells with similar efficiency without evident neurotoxicity. Given that humans do not present pre-existing immunity against BVs, BV may constitute a valuable tool for delivery of therapeutic genes in the brain.

0896 - LOOKING FOR DRUG SYNERGY AGAINST CANCER THROUGH POLYAMINE METABOLISM IMPAIRMENT: INSIGHT THE METABOLIC EFFECT OF INDOMETHACIN OVER KRAS-MUTATED LUNG CANCER CELLS.

Rodrigo LÓPEZ | Fredy LOPEZ-CONTRERAS | Matias MUÑOZ-URIBE | Jorge PEREZ-LAINES | Laura ASENCIO-LEAL | Andres RIVERA-DICTTER | Antonia MARTIN-MARTIN | Rafael BURGOS | Pablo ALARCON

UNIVERSIDAD AUSTRAL DE CHILE

Abstract/Resumen: Non-small cell lung cancer (NSCLC) is the most lethal and prevalent lung cancer type. Mutations in the

Kirsten rat sarcoma viral oncogene homolog (KRAS) gene are present in approximately 25 % of patients with NSCLC. The levels of polyamines (putrescine, spermidine, and spermine) are increased in cancer, being pivotal for tumor proliferation. Indomethacin (INDO) increases the abundance of an enzyme termed spermidine/spermine-N1-acetyltransferase (SSAT, encoded by the SAT1 gene), a key player in the catabolism of polyamines. Consequently, our aim was to investigate the effect of INDO in two NSCLC cell lines, with different KRAS mutation status. A549 and H1299 NSCLC cells (KRAS-mutated and wild-type, respectively) were exposed to INDO. Evaluations included SAT1 expression, SSAT levels and GC/MS metabolomics. Also, levels of polyamine synthesis enzymes and the synergistic effect of INDO and inhibitors of these enzymes were investigated. INDO increased the SAT1 expression and SSAT levels in both cell lines. In A549 cells, INDO significantly reduced the levels of putrescine and spermidine and increase the metabolic features upstream of the polyamine pathway (i.e., ornithine and methionine). However, in H1299 cells, the metabolic impact of INDO was non-significant. Regarding the polyamine synthesis enzyme levels, we found that ornithine decarboxylase (ODC) is increased in A549 cells, whereas S-adenosylmethionine-decarboxylase (AMD1) and polyamine oxidase (PAOX), are increased in H1299 cells. This observation correlated with relative resistance to the drugs DFMO, SAM486, and MDL72527 (inhibitors of ODC, AMD1, and PAOX, respectively). Finally, INDO had synergistic effect with MDL72527 in A549 and with SAM486 in H1299 cells. These results indicate that INDO alters polyamine metabolism in NSCLC cells and enhances the effect of polyamine synthesis inhibitors. However, these effects could vary depending on the genetic background of each NSCLC cell type.
Supported by FONDECYT 1160807 grant.

0917 - EVALUATION OF MUSCARINIC RECEPTORS GENE EDITING BY CRISPR/CAS9 ON MIGRATION, SPHEROID GROWTH AND ANGIOGENESIS IN HUMAN BREAST CANCER CELLS.

Adriana Marcela MARTINEZ PEREZ (1) | Dileyvic GIAMBALVO GÓMEZ(2) | Alejandra NOZYCE(2) | Agustina ORABONA(2) | María Gabriela LOMBARDI(2)

CENTRO DE ESTUDIOS FARMACOLÓGICOS Y BOTÁNICOS (CEFYBO), UNIVERSIDAD DE BUENOS AIRES-CONICET (1); CEFYBO, UBA-CONICET (2)

Abstract/Resumen: It has been reported that muscarinic receptors (M) are absent in normal breast cells and are up-regulated in tumor cells. Particularly, human breast cancer MCF-7 cells express M3 and M4 subtypes and its activation promotes cancer progression. We demonstrated that M expression in non-tumorigenic human mammary cell lines triggers malignant transformation. To confirm the contribution of M on tumoral progression, we developed new cell lines by genome editing of M3 and/or M4 receptors in MCF-7 cells using specific CRISPR-Cas9-gRNA complexes (cM3, cM4 and cM3M4). We analyzed the effect on cell migration capacity by wound healing assay, on the ability to generate three-dimensional structures (spheroids) in vitro and on induced angiogenesis in vivo. All cM cell lines significantly decreased their migration capacity (cM3: 67 ± 2; cM4: 77 ± 0.4 and cM3/4: 36.5 ± 6.7 %; n= 3) in comparison with MCF-7 cells (considered as 100 %, $p<0.0001$). Spheroids were formed using the hanging droplet method. All cM cell lines were able to form spheroids, however their growth kinetics were slower than MCF-7 spheroids, especially cM3M4. Tumor induced angiogenesis was quantified inoculated $2x10^5$ cells of different experimental groups in female NUDE mice. After 5 days, the animals were sacrificed and angiogenesis was quantified in the sites of inoculation as vessel density. The pretreatment with carbachol increase angiogenic response of inoculated MCF-7 cells in comparison to control (6.4 ± 0.7 vs. 3.3 ± 0.7, $p<0.0001$). The specific gene editing of M receptors in MCF-7 cells treated with carbachol significantly reduced neovascularization capacity of tumoral cells (cM3: 4.8 ± 0.5*; cM4: 3.8 ± 0.6**; cM3M4: 3.4 ± 0.5** vs. MCF-7 *$p<0.01$, ** $p<0.0001$). In conclusion, the specific M gene edition by CRISPR-Cas9 system in tumoral MCF-7 cells can effectively reduce the effects of muscarinic activation on migration, spheroid growth and angiogenesis.

0920 - IMPLICATIONS OF THYROID HORMONES (TH) IN REXINOIDS ANTI-LYMPHOMA ACTIVITY: INTEGRIN ALPHA V BETA 3 INHIBITION IN THE TREATMENT OF T CELL LYMPHOMA (TCL) WITH BEXAROTENE

Maria Mercedes DEBERNARDI | Johanna Abigail DÍAZ ALBUJA | Helena Andrea STERLE | Maria Celeste DIAZ FLAQUE | Graciela Alicia CREMASCHI | Maria Florencia CAYROL

BIOMED. UCA

Abstract/Resumen: Bexarotene (Bex), a RXR agonist used for cutaneous TLC treatment, is associated with clinical hypothyroidism, thus requiring the concomitant administration of levothyroxine (T4). We found that physiological levels of TH contribute to the malignant phenotype of TCL via the TH membrane receptor (mTR), the integrin alphaVbeta3. Here we investigated the consequence of T4 on the antineoplastic effect of Bex in different TCL subtypes. We confirm the presence of the RXR by WB in our panel of TCL subtypes. BEx effect in vitro on apoptosis and proliferation of CUTLL1, OCI-Ly12 and OCI- Ly13.2 TCL cells was higher in the absence than in the presence of TH supplementation ($p<0.05$). Also, we studied the impact of T4 addition to Bex treatment (BexT4+) in mice bearing a syngeneic TCL solid tumor and found that Bex decreased EL-4 tumor growth ($p<0.001$ vs. vehicle), being this effect even higher in the absence of T4 ($p<0.05$ vs. Bex). However, Bex alone decreased the anti-lymphoma immunity, as shown by a decrease of activated CD8+T-cells and of IFNg and TNFa tumor production ($p<0.05$ vs. BexT4+), thus T4 replacement is necessary to avoid a negative immunity. In a metastatic TCL murine model, we found that Bex alone decreased the number of experimental metastasis in the liver ($p<0.001$ vs. vehicle) and kidneys, this effect tends to be less pronounced in the presence of T4. Integrin alphaVbeta3 is overexpressed in TCL cells, so we investigated if its inhibition with cilengitide (Cil) would impair the pro-survival effect of TH and its role in Bex treatment. We demonstrated that mTR inhibition resulted in improved Bex-induced effects on apoptosis and cell proliferation in vitro in all TCL subtypes ($p<0.05$). Moreover, in vivo Bex+Cil combination render significantly smaller tumors ($p<0.001$ vs. vehicle and $p<0.05$ vs. BexT4+), while maintaining the anti-lymphoma immunity. Our results provide a rational method for evaluating the addition of Cil to treatments based on Bex and T4 supplementation for TCL.

0941 - PROGNOSTIC IMPACT OF IMMUNOHISTOCHEMICAL CHARACTERIZATION OF MARKERS OF BIOLOGICAL SUBTYPES IN RETINOBLASTOMA. PRELIMINARY RESULTS

María Del Rosario ASCHERO (1) | Daniela OTTAVIANI(2) | Gabriela LAMAS(3) | Santiago ZUGBI(1) | Ursula WINTER(1) | Ezequiel NÉSPOLI(3) | Daiana GANIEWICH(3) | Claudia SAMPOR(3) | Marcela MENA(1) | Andrea LLERA(1) | Paula SCHAIQUEVICH(1) | Fabiana LUBIENIECKI(3) | Guillermo CHANTADA(1)

HOSPITAL DE PEDIATRIA JUAN P GARRAHAN - CONICET (1); INSTITUT CURIE (2); HOSPITAL DE PEDIATRIA JUAN P. GARRAHAN (3)

Abstract/Resumen: Retinoblastoma (RB) is the most frequent ocular tumor in childhood, its prognosis is based on the identification in the enucleated eye of high risk factors in pathology (HRPF) such as the invasion of the choroid, sclera and optic nerve. However, the risk of relapse is variable in the cohort of patients with HRPF. Results from our group obtained in studies of exome, transcriptome and methylome suggest the existence of two tumor subtypes called cone and mixed, which may be identified by the expression of two markers ARR3 and TFF1 by