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EDITORES RESPONSABLES

Claudia Pérez Leirós
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AND AS160 EXPRESSION THROUGH PI3K/AKT PATHWAY IN ARPE-19 CELLS EXPOSED TO HIGH GLYCEMIA

Constanza Potilinski¹, Micaela Petrigliano¹, Gustavo Ortiz¹, Juan Gallo¹

¹Instituto de Investigaciones en Medicina Traslacional (IIMT) - CONICET, Universidad Austral

Diabetic retinopathy (DR) is associated with persistent inflammation and with damage to the vascular bed. The ophthalmic therapy for this retinal disease is focused on severe stages of the illness. Previous results obtained by our group show that Alpha-1 Antitrypsin (A1AT) acts like an anti-inflammatory agent that could play a role on DR treatment. However, it is important to know the effect of A1AT on proteins that are relevant to retinal function and the molecular mechanisms involved. The retinal pigment epithelium (RPE) forms the outer component of the blood-retinal barrier. Connexin43 is a major gap junction protein expressed in RPE cells. Cx43 upregulation have been implicated in edema and loss of vascular integrity, leading to neuronal death. AS160 is involved in insulin signaling affecting GLUT proteins.

We evaluated Cx43, NFκB and AS160 expression and proteins implicated in different signaling pathways in an in vitro diabetic retinopathy cell model.

ARPE-19 cells (ATCC® CRL-2302TM, USA) were maintained in DMEM/F12 (Invitrogen, USA) containing 2μM L-glutamine, 100U/ml penicillin, 100μg/ml streptomycin, and 10% fetal bovine serum. ARPE-19 cells (passages 9-12) were incubated 16h with DMEM 5.5mM glucose (Control), DMEM 5.5mM glucose + 4.5mg/ml A1AT (Control + A1AT), DMEM 30mM glucose (Diabetic), DMEM 30mM glucose + 4.5mg/ml A1AT (Diabetic + A1AT). Cells were harvested with RIPA for Western blot or fixed for immunohistochemistry.

A1AT diminished levels of Cx43 and AS160, A1AT also reduces AKT and pAKT1/2/3 expression levels, indicating PI3K/AKT pathway participation, and a possible crosstalk with Wnt and Insulin signaling. Besides, we could also observe a lower expression of NFκB p65 and iNOS, both proteins involved in the inflammatory response.

Results support the hypothesis that A1AT regulates Cx43 and AS160 expression through PI3K/AKT, Wnt and Insulin signaling pathway. Taking together, these results indicate that A1AT is a promising molecule to treat DR.

80. (751) ADESMIA BORONIOIDES AND SOLIDAGO CHILENSIS, TWO NOVELS HERBAL INFUSIONS WITH TOXIC EFFECTS AGAINST COLON CANCER DERIVED CELLS

Bruno Gastaldi, Yanina Andrea Assef³, Silvia Beatriz González, Gabriela Inés Marino

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The development and progression of colon cancer is strongly influenced by diet substances that enter in the digestive tract. Herbal infusions from medicinal plants usually contains phytochemicals that can restrain the development and progression of colon cancer in various ways. Flavonoids, an important group of these phytochemicals, report a recognized anti-inflammatory, antioxidant and signal-regulating properties. Adesmia boronioides and Solidago chilensis are two native medicinal plants that contain flavonoids and have reported promising antiproliferative activity against T-84 cells. Our aim was to study the toxic effects of herbal infusions obtained from A. boronioides and S. chilensis on Caco-2 and HT-29 cells as models of colon cancer.

We observed by MTT assay (after 72 h) that the percentage of viable cells decreased with the increase in the concentration of freeze-dried infusions of both plant species (0 to 50 mg/ml) ($p < 0.05$, $n = 3$). S. chilensis had a higher antiproliferative effect (EC50 (mg/ml): 0.57 ± 0.06 and 0.18 ± 0.02) in comparison with A. boronioides (EC50 (mg/ml): 1.27 ± 0.08 and 2.87 ± 0.21), for Caco-2 and HT-29 cells, respectively. Colchicine was used as positive control. Similar results were obtained by Trypan blue exclusion technique ($p < 0.05$, $n = 3$). After staining the cells with AO and EtBr, apoptosis cells

(orange cells) were observed under the fluorescence microscope. The basal apoptotic percentage (24h) was increased in A. boronioides (35.0 ± 4.1 and $46.2 \pm 8.2\%$) and in S. chilensis (47.2 ± 6.7 and $35.8 \pm 4.0\%$) with respect to control (3.8 ± 4.9 and $2.7 \pm 3.1\%$) in Caco-2 and HT-29, respectively ($p < 0.05$, $n = 3$). The Procaspase-3 expression was also checked.

We conclude that the infusion of the both species exert strong antiproliferative activity on cells derived from colon cancer, partly due to the modulation of basal apoptosis. Its effects show to be much greater in comparison with other species studied. These results provide a direction for further researches about the antitumoral potential of these native plants.

81. (570) DEVELOPMENT OF THERAPEUTIC IMMUNORADIOPHARMACEUTICALS BASED ON CAMELID NANOBODIES (VHH) AGAINST EGFR

Julia Milena Gallino Fernández¹, María Belen Cerda¹, Marisa Trotta¹, Ana Clarisa Bularte¹, Alfredo Miguel Zapata¹, Florencia Giannoni¹, Rodrigo Lloyd¹, Sofia Aguilar¹, Osvaldo Podhjaccer³, Noemi Nelida Nevares¹, Jose Luis Crudo¹, Lucia Policastro¹

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Radioimmunotherapy (RIT) is a type of cancer cell targeting therapy which uses monoclonal antibodies against tumor-associated antigens labeled with radionuclide. The epidermal growth factor receptor (EGFR) is often overexpressed in various types of human cancers, for which it is a good antigen to be used in RIT. Lutetium-177 (Lu-177) has a half-life of 6,7 days and a maximum negative beta emission of 497 KeV. Hence, this radionuclide is ideal for therapeutic radiopharmaceuticals developments. The aim of this work is to develop novel Lu-177 radiopharmaceuticals based in camelid nanobodies or VHH. We propose to label a VHH against EGFR (VHH-EGFR) with Lu-177 to treatment EGFR(+) tumors. At this stage, we have obtained VHH-EGFR and labeled it with Lu-177, which was generated in the Centro Atómico Ezeiza. Previously, VHH-EGFR was conjugated to the bifunctional chelating agent pSCN-Bn-DTPA in order to label it by Lu-177. The specific activity of 177Lu-VHH-EGFR radiopharmaceutical was of 2,11 mCi/mg and the radiochemical purity was of 99,2% at the time of purification and 80,6% seven days later. We used different EGFR (+) or EGFR (-) human tumor cell lines in order to prove the selectivity of our radiopharmaceutical. In addition, cells were blocked for 2 h with cold Cetuximab (monoclonal antibody against EGFR) as negative control. After that, cells were exposed to radiopharmaceutical for 4 and 24h at 37 °C. Fractions of non-internalized (supernatant and washed with PBS) and cell-associated (washed with trypsin) were collected. The fractions were manually measured in a well-glass radiometric detector. As conclusion we obtain 177Lu-VHH-EGFR with high specific activity and high radiochemical purity that was able to bind selectively to EGFR(+) cells lines. In future experiments, we will advance improving the affinity of the VHH-EGFR, obtaining a bivalent VHH-EGFR, which will also be labeled with Lu-177 and compared with the monovalent VHH-EGFR.

INMUNOLOGÍA / IMMUNOLOGY 1

82. (27) IMMUNE-MEDIATED INFLAMMATION PROMOTES SUBCLINICAL ATHEROSCLEROSIS IN RECENT-ONSET PSORIATIC ARTHRITIS PATIENTS WITHOUT CONVENTIONAL CARDIOVASCULAR RISK FACTORS

Rodolfo Kolliker Frers¹, Matilde Otero-Losada¹, Adriana Urdapilleta², Vanesa Cosentino², Julia Tau², Eduardo Kerzberg², Sabrina Porta², Monica Chioconci², Nora Kogan², Francisco Capani¹

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Objectives. To evaluate markers of cardiovascular risk in cutaneous psoriasis (CPs) and recent-onset PsA patients.