2017

medicina

BUENOS AIRES VOL. 77 Supl. I - 2017

MEDICINA

Volumen 77, Supl. I, págs. 1-620

medicina

BUENOS AIRES, VOL. 77 Supl. I - 2017

La Tapa (Ver p. IV)
Imagen ígnea, 1996.
María Esther Gené

MEDICINA (Buenos Aires) – Revista bimestral – ISSN 1669-9106 (En línea)

REVISTA BIMESTRAL
Registro de la Propiedad Intelectual N° 5324261
Personería Jurídica N° C-7497
Publicación de la Fundación Revista Medicina (Buenos Aires)
Propietario de la publicación: Fundación Revista Medicina
Queda hecho el depósito que establece la Ley 11723

Publicada con el apoyo del Ministerio de Ciencia, Tecnología e Innovación Productiva.
MEDICINA no tiene propósitos comerciales. El objeto de su creación ha sido propender al adelanto de la medicina argentina. Los beneficios que pudieran obtenerse serán aplicados exclusivamente a este fin.
Aparece en *MEDLINE (PubMed), ISI-THOMSON REUTERS (Journal Citation Report, Current Contents, Biological Abstracts, Biosis, Life Sciences), CABI (Global Health), ELSEVIER (Scopus, Embase, Excerpta Medica), SciELO, LATINDEX, BVS* (Biblioteca Virtual en Salud), *DOAJ, Google Scholar y Google Books.*
Incluida en el Núcleo Básico de Revistas Científicas Argentinas del CONICET.

Directores Responsables:
Basilio A. Kotsias, Damasia Becú Villalobos, Isabel Narvaiz Kantor, Guillermo B. Semeniuk

Secretaría de Redacción: Ethel Di Vita, Instituto de Investigaciones Médicas Alfredo Lanari, Combatientes de Malvinas 3150, 1427 Buenos Aires, Argentina
Tel. 5287-3827 Int. 73919 y 4523-6619
e-mail: revmedbuenosaires@gmail.com – http//: www.medicinabuenosaires.com

Vol. 77, N° 5, Noviembre 2017

Edición realizada por
GRAFICA TADDEO – Charrúa 3480 – Buenos Aires – Tel: 4918.6300 l 4918.1675 l 4918.0482
e-mail: ctp@graficataddeo.com.ar – www.graficataddeo.com.ar

medicina
BUENOS AIRES, VOL 77 Supl. I - 2017

REUNIÓN CONJUNTA DE SOCIEDADES DE BIOCIENCIAS

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

LIII REUNIÓN ANUAL DE LA SOCIEDAD ARGENTINA DE INVESTIGACIÓN BIOQUÍMICA Y BIOLOGÍA MOLECULAR (SAIB)

LXV REUNIÓN ANUAL DE LA SOCIEDAD ARGENTINA DE INMUNOLOGÍA (SAI)

REUNIÓN DE LA SOCIEDAD ARGENTINA DE ANDROLOGÍA (SAA)

XLVI REUNIÓN ANUAL DE LA SOCIEDAD ARGENTINA DE BIOFÍSICA (SAB)

XIX REUNIÓN ANUAL DE LA SOCIEDAD ARGENTINA DE BIOLOGÍA (SAB)

XLIX REUNIÓN ANUAL DE LA SOCIEDAD ARGENTINA DE FARMACOLOGÍA EXPERIMENTAL (SAFE)

REUNIÓN ANUAL DE LA SOCIEDAD ARGENTINA DE FISIOLOGÍA (SAFIS)

REUNIÓN DE LA SOCIEDAD ARGENTINA DE HEMATOLOGÍA (SAH)

XXIX REUNIÓN ANUAL DE LA SOCIEDAD ARGENTINA DE PROTOZOOLOGÍA (SAP)

13-17 de noviembre de 2017
Palais Rouge– Buenos Aires

Silvina Villar (1), Oscar Bottasso (1), Silvana Virginia Spinelli (1)
(1) IDICER CONICET-UNR. (2) Servicio de Neumonología. Hospital Provincial del Centenario. (3) Laboratorio Central. Hospital Provincial del Centenario

Resistance to corticosteroids in patients with severe asthma and with chronic obstructive pulmonary disease (COPD) is an important barrier to an effective treatment. Different lines of evidence indicate that glucocorticoids (GCs) resistance is the result of significant changes in the cellular microenvironment that occur over time during disease progression. Several factors have been involved in this process and recent findings indicate that miRNAs may also be playing a role in the development of GC resistance during chronic inflammatory states. In this work we contribute to the characterization of the immunoendocrine interactions observed in patients with both severe asthma and COPD as a preliminary approach to subsequent studies on the role of sRNA in the development of GC resistance in these diseases. Both sputum and blood samples from volunteers (n=20) were employed to compare the events occurring at the lung with what happens in the peripheral compartments. As expected, most asthmatic patients, and some with COPD showed abnormally high IgE blood levels and mild leukocytosis, with elevated eosinophils. Interestingly, in most cases sputum cytology did not show an eosinophilic infiltrate and neither of these findings correlated with the severity/stage of the diseases. Levels of endogenous cortisol were also quantified to confirm that there is no adrenal suppression in these patients despite treatment with inhaled corticosteroids. Also, RNA was purified from both sputum and blood samples and CG receptor transcript and miR-223, let-7 and tRNAh Glu were quantified by RT-qPCR, being able to detect sRNAs in all analyzed samples, including extracellular fractions. In summary, these results provide a first approach for the better understanding of the immunoendocrine alterations associated with pulmonary obstructive diseases and present a useful experimental design for the study of regulatory mechanisms mediated by miRNAs in secretions of patients with asthma and COPD.

Keywords: asthma, COPD, sRNA, glucocorticoids

(764) **HYPOGONADISM IN MEN WITH STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD). ASSOCIATION BETWEEN TESTOSTERONE AND COPD SEVERITY. CROSS SECTIONAL STUDY**

Sebastián Matías Suárez (1), Pablo René Costanzo (1), Pablo Knoblovits (1), Joaquín Maritano Furtada (1), Juan Arturo Precerutti (1), Horacio Matías Castro (1)
(1) Hospital Italiano de Buenos Aires.

The prevalence of hypogonadism in patients with COPD is estimated in 22-69%. The association between testosterone (T) levels and COPD severity is controversial. Aim: To estimate the prevalence of hypogonadism in men with stable COPD and the association between T and COPD severity. Methods: 47 men, 69.1±8.9 years and BMI: 27.8±4.3 kg/m^2 were included. COPD severity was evaluated with BODE index. Laboratory: total T(TT), estradiol (E2), LH, SHBG and prolactin.Free (FT) and bioavailable T (BT) were calculated. ADAM and IIEF-5 score were performed. Hypogonadism was considered when TT<3 ng/ml, FT<6.1 ng/ml or BT<1.2 ng/ml. Results: Laboratory (X±SD): TT 3.3±1.3 ng/ml, FT 5.4±1.8 ng/ml, BT 1.2±0.4 ng/ml, LH 4.2±2.1 mU/ml, SHBG 46.1±18.8 nmol/l, E2 24.9±7.4 ng/ml and prolactin 8.2±3.5 ng/ml. Hypogonadism: TT 48.9%, FT 63.8%, BT 42.6%. ADAM score was positive in 80.9% patients, 38.3% in those with TT>3 ng/ml and 86.7% in those with TT<3 ng/ml. IIEF-5 was performed in 28 patients, 82.1% had erectile dysfunction. A negative correlation between BODE index and TT: -0.28, p=0.05; FT: -0.38, p=0.007 and BT: -0.39, p=0.0065, was found. Conclusions: Men with stable COPD have a high prevalence of biochemical and clinical hypogonadism. ADAM score has a high sensitivity and a low specificity, T measurement is recommended. T values have a negative correlation with the severity of COPD, lower T are associated with high severity.There is a high prevalence of erectile dysfunction in this population.

Key words: hypogonadism, chronic obstructive pulmonary disease

(1399) **HYPERCOAGULABLE STATE AND RISK OF TROMBOSIS IN THE DOG WITH CUSHING'S DISEASE**

Patricia Noemí Vidal, Diego Daniel Miceli, Víctor Alejandro Castillo
Facultad de Cs. Veterinarias - Hospital Escuela de Pequeños Animales - UBA, Unidad de Endocrinología.

Hypercoagulable state is a situation of high morbidity and mortality in the dog with Cushing's Disease (EC). The most serious condition is pulmonary thromboembolism which is a cause of death. D-dimer (DD), a degradation product of fibrin, is an indicator of thrombosis. The Von Willebrand Factor (FvW) and the inhibitor of plasminogen activator-1 (PAI-1), are increased in plurimetabolic syndromes. The objective of this study was to evaluate whether the activity of Antithrombin III (ATIII) and DD are useful as indicators of formation or presence of thrombosis and to analyze the concentrations of FvW and PAI-1 in the dog with EC compared to a group of healthy dogs. We studied a total of 26 dogs with EC. To make the comparison 12 of them were taken and then 12 dogs from the bioterior, as a control group. All patients underwent platelet counts, coagulation times (KPTT and prothrombin time (PT)), fibrinogen (F), ATIII expressed as ATIII activity (normal> 80%) and DD (positive> 200, DD +). FvW and PAI-1 were measured by ELISA. Proteinuria in relation to creatinine (PRC, normal value <0.30). Results were expressed as average ± SEM, the comparison of the averages were made by the t-test of unpaired samples. P <0.05 was considered significant. Fisher's Test was also used. The platelet count, KPTT, TP and F were normal. In 9/26 (34.6%) both the ATIII and the DD were altered, with an inverse correlation (r = -0.5). The PRC was elevated in 10/26 (38.5%), associating with the lowest ATIII activity and DD +, PRC values correlated with ATIII (r = -0.75) and with DD (r = 0, 67). The concentrations of FvW and PAI-1 were significantly higher in the group with EC (FvW: 4,2±0,3 vs 2,7±0,3 ng/ml; PAI-1: 836,6±153,2 vs 295,2±24,1 pg/ml). Routine coagulation studies aren't relevant for diagnosing thrombosis. The increase in FvW and PAI-1 shows the presence of hypercoagulability and higher risk of thrombosis. The evaluation of DD and ATIII is recommended for the diagnosis of thrombosis.

Keywords: Hypercoagulable - Cushing's Disease – Thrombosis - Von Willebrand Factor - Inhibitor of plasminogen activator-1

HEMATOLOGY 1

(1355) **COORDINATED REGULATION OF HEPCIDIN AND IRON IMPORTERS THROUGH IRON EXCESS AND ERYTHROPOIETIN SIGNALS IN ENTEROCYTE AND HEPATOCYTES IN MICE MODELS.**

Gisela Giorgi, Florencia Fernandez Delías, Marta Roque
Fisiología Humana. Biología, Bioquímica y Farmacia. Universidad Nacional del Sur-CONICET-INBIOSUR. Bahía Blanca.

The erythropoietic activity is the main inhibitor of the hepcidin expression, the key regulator of the iron metabolism that reduces the intestinal absorption of iron and the release from macrophages. **Objective:** To evaluate the response of functional axis "HEPCIDIN-DMT1-ZIP14 using mice models of iron-overload and also an erythropoiesis induced by EPO. **M*aterials and Methods*:** CF1 mice (25±5g) were divided into 4 groups (n=4/group;block design):1)*Iron-overload and* erythropoietin(IO+EPO) Fe-Saccharate ip (days 0,4,8,12;1800mg/kg) and EPO ip(days 17,18,19;20000UI/kg);*2)Iron-overload*(IO);3)Erythropoietin(EPO);4*)control (C).*The Protocol was approved by the Committee on Experimental Animal Use and Care-UNS. Immunohistochemistry: DMT1, ZRTIre like protein14 (ZIP14),prohepcidin,ferritin. **Results:** *Duodenum:* In control and EPO, ZIP14 was found in enterocytes apical membrane, while a slight basolateral expression was seen in iron-overload with and without EPO. DMT1 in enterocyte cytoplasm was moderated in Control, while in Iron-overload it was slight. In EPO and IO+EPO, the apical DMT1 was intense. *Liver:* The prohepcidin expression was slight in EPO, moderated in control and intense in IO and IO+EPO. Both ZIP14 and ferritin in hepatocyte cytoplasm were weak in C and in EPO, they were intense in iron-overload and IO+EPO.

Evident DMT1 expression was detected in the cell membrane and in cytoplasm of hepatocytes in EPO, while a weak expression was observed in C. In IO+EPO and IO, DMT1 expression was slight in hepatocytes cytoplasm. **Conclusions:** Two signals could induce specific response for each group: (i) *iron-signal,* induced prohepcidin synthesis**,** which reduced the duodenal iron uptake through DMT1 and ZIP14 and increased the hepatic iron storage through ZIP14, reducing iron availability; (ii) *EPO-signal,* which affected duodenal iron uptake by DMT1 and, therefore, allowed an iron supply to the bone marrow.

Key words: erythropoiesis, iron-overload, mice models, enterocytes, hepatocytes.

(1393) **PROTEINS ASSOCIATED TO UPTAKE OF IRON IN HUMAN NEUROBLASTOMA CELLS**

Florencia Fernandez Delías (1), Gisela Giorgi (1), Daniela Vittori (2), Marta Roque (1)
(1) Fisiología Humana. Biología, Bioquímica y Farmacia. Universidad Nacional del Sur-CONICET-INBIOSUR. Bahía Blanca. (2) Universidad de Buenos Aires, Facultad de Ciencias Exactas y Naturales, Departamento de Química Biológica. CONICET-IQUIBICEN.

Introduction: Alterations in the neuronal iron uptake are frequently associated to brain diseases. Therefore, the aim was to study the effect of iron excess on divalent metal transporter1 (DMT1) and Zrt-Irt-like Protein14 (ZIP14) expressions in human neuroblastoma cells. Materials and Methods: To evaluate cellular viability a dose-response curve was assayed with low and high iron concentrations (ferric ammonium citrate-FAC) 30μM-80μM and 200μM-600μM, respectively at different times. The iron uptake was assessed in the culture medium in 30μMFAC/72hs and in 600 μM/24hs treatments. Pre-treated cells with NAC 2Mm/12hs plus FAC30μM/72hs for immunocytochemistry: DMT1, ZIP14, prohepcidin, ferritin. Viability was assessed by a nuclear red method. Iron levels: Wiener kit. Results: In treatments with low FAC concentrations (30μM, 60μM and 80μM) it was observed a decrease in cellular viability at 72hs ($p<0,05$). However, in treatments with high FAC concentrations (450μM and 600μM), the decrease in the cellular viability was seen at 24hs($p<0,05$). The iron content in the culture medium decreased by 25% in 600μM-24hs and by 42% with 30μM/72 hs treatments. The ZIP14, prohepcidin and ferritin expressions were higher in cells with FAC 30μM/72hs compared with those found in the control. The DMT1 immunoreactivity was lower in cells with FAC30μM/72hs than that observed in the control. The NAC pre-treatment reversed the change induced by the iron in the ZIP14, the prohepcidin and the ferritin expressions. Conclusions: The increase in the ZIP14 expression could reflect a high iron uptake that produced neuronal death, being DMT1 the transporter without a relevant role. The high prohepcidin expression could suggest a decrease of iron export through deregulation of axis hepcidin-FPN. Thus, the change of the ZIP14 expression in neurons could be one of the mechanisms that produce neuronal death by high iron uptake.

Key Words: Iron, Neuroblastoma Cells, Hepcidin, Divalent Metal Transporter 1, Zrt-Irt-Like Protein14

(440) **ASSOCIATION BETWEEN GENOMIC REARRANGEMENTS AND INSTABILITY IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA**

Micaela Palmitelli (1, 2), Flavia Stella (2), Andrea Kryzswinski (2), Irma Slavutsky (2), Marcela Gonzalez Cid (1, 3)
(1) Laboratorio de Mutagénesis. (2) Laboratorio de Genética de Neoplasias Linfoides, Instituto de Medicina Experimental, CONICET-Academia Nacional de Medicina. (3) Instituto de Medicina Experimental, CONICET-Academia Nacional de Medicina.

Chronic lymphocytic leukemia (CLL) is a heterogeneous disease with a highly variable clinical course. Genomic instability (GI), evidenced by acquired genetic aberrations, has an important role in CLL pathogenesis, as the number of genomic alterations was shown to increase throughout the course from newly diagnosed to progressive and further to relapsed CLL. GI can be assessed by means of chromosome aberrations (CA) and micronucleus (MN) analysis. Cytogenetic and FISH (fluorescence in situ hybridization) studies are important prognostic factors in CLL. We have analyzed GI in 81 untreated CLL patients (41 males; mean age: 65.6 years; range: 42-83 years) and 6 normal controls. Cytogenetic analysis was performed on stimulated peripheral blood lymphocyte cultures. FISH was performed using the CLL panel according to manufacturer's protocol. For each patient, CA was evaluated on 50 metaphases while 250 interphase nuclei were analyzed for MN frequency. An increased number of CAs in CLL patients compared to controls (6.89±5.4% vs 0.25±0.4%, $p=0.004$), with the higher value in cases with abnormal (8.54±5.8%) vs normal (5.2±4.5%) karyotype ($p=0.008$), was observed. Considering FISH risk groups, the analysis showed a higher frequency of CA in patients with deletions 11q22/17p13 (8.4±5.6%) associated to poor prognosis than those with no alterations or deletion 13q14 (5.1±3.8%) ($p=0.012$) related to a better outcome, and +12 (3.6±2.3%) with intermediate risk ($p=0.010$). MN analysis displayed an increased frequency in CLL patients (3.1±1.7%) compared to controls (0.7±0.3%) ($p=0.001$) but no significant differences between cytogenetic or FISH groups were observed. Our results show the presence of basal genomic instability in untreated CLL patients as measured by both CA and MN techniques, as well as an association with cytogenetic and FISH risk groups, being to our knowledge the first study taking into account these prognostic factors.

Keywords: chronic lymphocytic leukemia, genomic instability, FISH, cytogenetic analysis.

(1232) **CANONICAL AND NON-CANONICAL STIMULATION OF T-ALL TUMOR CELLS AND MESENCHYMAL STROMAL CELLS DETERMINES TUMORAL NICHES WITH DIFFERENTIAL BEHAVIOR**

Mariana Amoros (1), Florencia Cayrol (2), Luciana Gutiérrez (1), Juan Bayo (3), Ricardo Farias (4), Leandro Cerchietti (5), Mariana Garcia (3), Carlos Luzzani (6), Santiago Miriuka (6), Alejandro Correa (7), Graciela Cremaschi (2), Marcela Bolontrade (1)
(1) Laboratorio de Células Madre, IByME-CONICET, (2) Lab Neuroinmunomodulación y Oncología Molecular, BIOMED-UCA-CONICET, (3) Laboratorio de Terapia Génica, Facultad de Ciencias Biomédicas, Universidad Austral, (4) Universidad Nacional de Tucumán, (5) Weill Cornell Medical College of Cornell University, New York, (6) Fleni, (7) ICC/ Fiocruz Paraná - Fundação Oswaldo Cruz

T-cell acute lymphoblastic leukemia (T-ALL) constitutes 20% of diagnosed ALL. As other hematological tumors it presents a close connection with the stromal counterpart. Leukemia cells can adjust the niche affecting the communication between the stroma and HSC in models of T-ALL. Thyroid hormone (TH) modulation may be critical in determining cancer progression. In this context we investigated the acquired functional behavior of mesenchymal stromal cells (MSC) when regulated by T-ALL cells in a TH-modulated microenvironment. We demonstrated that TH stimulation on T-ALL cells via surface receptors (non-canonical TH action) induced a higher chemotactic response and stronger morphogenic rearrangements, while canonical TH stimulation on tumor cells induced less chemotactic response (1.5 fold higher, 148±23 MSC/field, $p<0,05$) and less morphogenic rearrangements in MSC. Further, direct stimuli exerted by canonical TH on MSC induced higher MMP2 activity (1,55±0,25 vs. 1,24±0,15 MMP2 relative activity, $p<0,01$) and a high secretory activity via microvesicles (MV) on these cells (0,44 ug/ml/cm2 vs. 0,3 ug/ml/cm2). We proposed based on the outlined data a working model where canonical TH stimulation generates a niche that induces MSC to stay and rearrange the tumor microenvironment, while non-canonical TH stimulation generates a tumor microenvironment with MSC more prone to leave the niche. Thus, signaling triggering a prevailing canonical or non-canonical TH action could be critical in determining a tumoral niche of T-ALL cells interacting with MSC.

(885) **SMC3 HAPLOINSUFFICIENCY RESULTS IN GERMINAL CENTER HYPERPLASIA AND COOPERATES WITH BCL6 TO INDUCE B-CELL LYMPHOMA**