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.
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Incluida en el Núcleo Básico de Revistas Científicas Argentinas del CONICET.

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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

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

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timeric complex that collaborate with chaperons. In certain complexes, the presence of Ca+2 is essential for an adequate protein folding. As a result, we hypothesize that *Tc*CAL1 can modulate the function of these proteins in different processes. Current work concerns the validation of *Tc*CAL1 associations in co-immunoprecipitation assays from *T. cruzi* extracts. Future work involves studies of *Tc*CAL1 deregulation and their effect on differentiation and infection, in order to establish its role in these processes.

Keywords: Ca+2 binding protein, *Trypanosoma cruzi*

(393) **CHARACTERIZATION OF *Trypanosoma cruzi* ALPHA-TUBULIN ACETYLTRANSFERASE**

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Among the numerous isoforms of α-tubulin found in the different microtubular structures of *Trypanosoma cruzi*, acetylated α-tubulin is one of the most abundant. In other organisms, one of the enzymes responsible for this modification is the α-tubulin acetyltransferase, or αTAT.

We have identified a coding sequence for the putative αTAT in the genome of *T. cruzi*, established lines that overexpress the protein of interest in an inducible manner, using the pTcINDEX-GW vector and characterized the mutant parasites phenotypically. As a first approach, we evaluated the overexpression of the αTAT in the mutants by western blot analysis (using anti-α-tubulin and anti-acetylated α-tubulin as primary antibodies), showing an increase in the levels of tubulin acetylation when αTAT is overexpressed. Besides, other experiments indicated that the protein localizes mainly in the cytoskeleton and flagellum of *T. cruzi*. Subsequently, we studied the growth of the mutant epimastigotes and a remarkable reduction was observed as a result of an increased expression of αTAT. Furthermore, we studied the morphology of the mutants by phase contrast microscopy and immunofluorescence analysis. The overexpression of αTAT led to an abnormal morphology in the parasites; aberrant nuclei and parasites containing more than one flagellum were observed. In addition, a higher concentration of the protein was detected mainly in the perinuclear region. Finally, we evaluated the phenotypic effect generated by orizalyn, a microtubule depolymerizing drug. Wild-type parasites lose their normal morphology after the treatment in a dose-dependent manner but differences in drug resistance were observed in the overexpressing parasites upon the induction.

These findings suggest that the mechanisms of tubulin modification –particularly acetylation- could influence the functional role of the microtubules, both in cell division and differentiation during the parasite's life-cycle.

Keywords: *Trypanosoma cruzi*, alpha-tubulin, acetylation, cytoskeleton

(1455) **CHARACTERIZATION OF HISTONE DEACETYLASE ENZYMES OF CESTODE PARASITES AS POTENTIAL DRUG TARGETS OF NEGLECTED DISEASES**

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Cestode parasites cause neglected diseases such as hydatidosis. These parasites have complex life cycles undergoing metamorphic events that comprise cell proliferation, differentiation and death. This suggests the involvement of a complex system of gene expression control that has been associated with changes in chromatin structure in trematode parasites. Histone deacetylase enzymes (HDAC) remove acetyl groups from histones and other cellular effectors, thus directly influencing the chromatin structure and thereby regulating gene transcription and other cellular processes. HDAC have been validated as drug targets for the treatment of cancer and other diseases including parasitic infections. However, knowledge of HDAC in cestode parasites is lacking. Previously, we have shown the presence and transcription of HDAC genes in several species of cestode parasites. In this work, we aimed to study the effect of the pan-HDAC inhibitor Trichostatin A (TSA) in *Mesocestoides corti*, a cestode laboratory model. We found a decrease in the viability, measured by AlamarBlue assay and motility index determination, and observed phenotypic alterations in *M. corti* larvae upon incubation with TSA. To assess the molecular target of TSA, we evaluated changes in the total amount of acetylated histone H4 by western blot using anti-acetylated histone H4 antibody. We observed a band corresponding to acetylated H4 histone in parasites treated with TSA but not in control parasites, suggesting that TSA strongly inhibits H4 histone deacetylation. This effect was not observed in parasites treated with praziquantel and albendazole suggesting a specific effect of TSA. These findings suggest that HDAC could have an essential role in cestode development and survival. This work provides a first step into the study of epigenetic mechanisms in cestode parasites and explores new alternatives to treat the diseases they cause.

Keywords: HDAC, neglected diseases, drug targets, cestode parasites.

(1055) **VIRTUAL SCREENING OF FLAVONOIDS AS POSSIBLE INHIBITORS OF *TRYPANOSOMA CRUZI* ARGININE KINASE.**

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Arginine kinase from *Trypanosoma cruzi* (*Tc*AK) is an enzyme involved in the energetic homeostasis and response to stressors in the parasite. The activity of enzyme, among some of its homologues from diverse phyla, is inhibited by some flavonoid compounds. In addition to it, one of these inhibitors, the resveratrol, affected the replication and survival of cultured epimastigotes as well as amastigotes/trypomastigotes infecting mammal cell cultures. In order to test other molecules that can throw light on the mode of interaction between the enzyme and the flavonoids, we arranged a simple pipeline that narrows the focus of the testing efforts to a handful of compounds.

For this, we downloaded the (now unavailable) database of medically active plant substances (MAPS), specifically the subset of flavonoid molecules, that comprised 326 compounds, and modeled the molecular interactions between these flavonoids and a homology model of *Tc*AK obtained from the iTASSER online server. These models were carried on two different molecular docking softwares, the open source AutoDock Vina, and the private licensed OpenEye.

Results from each software were ordered according to its docking score, and then both lists were compared to take only the molecules that were present between the best 100 scores of both programs, from which only 5 where shared among the first 20, 7 among the first 50 and 29 among e first 100. From these molecules, only 7 are purchasable, and three of them (delphinidine, malvidine and petunidine) were also present as possibly active compounds in the previous virtual screening that pointed out resveratrol as an inhibitor of the *Tc*AK activity, making them of high interest for future *in-vitro* tests.

Keywords: virtual screening, flavonoids, Arginine kinase, molecular docking

(1068) **DETECTION OF SPECIFIC IGE ANTIBODIES AGAINST *Trypanosoma cruzi* ARGININE KINASE.**

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The Arginine Kinase from *Trypanosoma cruzi* (*Tc*AK) is thought to be the product of gene transfer from an invertebrate host to a *Trypanosoma* ancestor. The function of this enzyme in the parasite is still unknown, but since it was found in extra-cellular *T. cruzi* vesicles, and it shares a very conserved sequence with invertebrate AKs, which are well known allergens in a very wide range of species, we suspect that *Tc*AK might have some immune modulating action by making immune response incline towards a Th2 response that is ineffective against the parasite, instead of a Th1 response that could control the infection.

To start testing this hypothesis we decided to measure the presence of *Tc*AK specific IgE antibodies in the serum of individuals infected and non-infected with the parasite. Samples were taken from individuals in Venezuela (49 Chagas positive and 46 Chagas negative) and in Argentina (20 positive and 10 negative), in order to take into account the regional differences in parasite strains and in host immune response. Detection was carried on by ELISA against recombinant *Tc*AK, using secondary anti-human IgE coupled with alkaline phosphatase and pNPP dephosphorilation. Results for each regional sera origin were obtained and treated separately, using for both groups a ROC curve and Mann-Withney test.

With both regional origins of the sera we found statistical significant differences in the *Tc*AK recognition between the non-infected and infected sera, with an Area Under the ROC curve >0,75 and a $p < 0,005$ for both the ROC analysis and the Mann-Withney test. These results points out that infection with the parasite trigers the production of IgE antibodies against *Tc*AK, but wether this priming of the response towards IgE secretion is relevant for the infection is still to be determined.

Keywords: IgE, Arginine kinase, Trypanosoma cruzi, ELISA.

IMMUNOLOGY (ADAPTIVE IMMUNITY) 2

(311) ***Chlamydia muridarum*** **INDUCE THE EXPRESSION OF CO-INHIBITORY MOLECULES ON IMMUNE CELLS**

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CIBICI-CONICET

Chlamydia trachomatis is the most commonly reported agent of sexually transmitted bacterial infections worldwide. This pathogen frequently leads to long-term persistent subclinical infections, both in male and female. This is in part due to certain mechanisms, not yet fully elucidated, that suppress the immune response to the pathogen. Recently, the role of co-inhibitory pathways in some chronic infections has been studied, and reports suggested that the overexpression of co-inhibitory molecules would be related to pathogen persistence. In the present work we aimed to evaluate the expression profile of co-inhibitory molecules using an *"in vitro"* model with *Chlamydia muridarum* (Cm) stimulation. For that purpose, splenocytes from C57BL/6 and NOD mice were in vitro stimulated for 24-48 h with inactivated Chlamydia Elementary Bodies at different bacteria/cell ratios. After that, PD-L1 and PD1 expression was determined by flow citometry in different cell subpopulations. A significant and dose dependent increase in the percentage of $PD\text{-}L1^{+}CD20^{+}$ lymphocytes was found after Cm stimulation when compared with non-stimulated cells ($P < 0.01$). Not only major percentages but also higher mean fluorescence intensity for PD-L1 were observed in B lymphocytes. Cm stimulation also induced higher percentages of $CD4^{+}PD\text{-}L1^{+}$ and $CD8^{+}PD\text{-}L1^{+}$ T lymphocytes, although in minor proportions when compared with B lymphocytes. Non-significant changes were observed in $CD11b^{+}$PD-L1+ and $CD11c^{+}$PD-L1+ cell populations. The expression of PD1 showed a similar pattern to those observed for PD-L1. Moreover, although B and T lymphocytes from C57BL/6 and NOD mice showed PD-L1 overexpression, the NOD strain showed a more pronounced response after Cm stimulation. Our results demonstrate that Chlamydia is able to induce the expression of co-inhibitory molecules mainly in B lymphocytes, possibly attenuating the immune response and favoring chronic and persistence infections in genital tract.

Keywords: Infection ,Co-inhibitory pathways, Chlamydia muridarum , PD-L1

(548) **REGULATORY T CELLS DYSFUNCTION IN INDIVIDUALS WITH TRISOMY 21**

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Trisomy 21 (T21) is the most common genetic disorder in human population, occurring in approximately 1 in 700 live births. Individuals with T21 have a unique disease spectrum and a hyperactivated Type I interferon signaling, which could be a result of increased gene dosage of the four IFN receptor subunits encoded on chr21. T21 causes widespread alterations in gene expression across the genome, including, most prominently, consistent activation of the interferon transcriptional response. Based on this and the fact that individuals with T21 are predisposed to develop autoimmune diseases, we decided to dissect Treg functionality in individuals with T21, focusing on the effect that the type I IFN-IFNAR axis could have on its biology. We characterized the circulating Treg cells and T cells subsets in individuals with or without T21 using multicolor Flow Cytometry. Individuals with T21 (n=9) have a significantly alteration in the CD4/CD8 ratio ($p<0,001$), and higher numbers of CD8+ T cells compared with controls (n=14, $p<0,05$). Also, these individuals present more CD8+ T cells that produce effector proteins (IFN-γ $p<0,05$ and GzmB $p<0,05$). When we focused on Treg cells, individuals with T21 have a higher number of CD4+Foxp3+ T cells in peripheral blood ($p<0,05$) but the expression of more than 20 phenotypic markers analyzed were similar to controls. Interestingly, individuals with T21 have an increased frequency of IFNAR1+ Treg cells ($p<0,05$). When an *in vitro* suppression assay was performed, a reduced inhibitory potential of Treg was clearly observed in individuals with T21, whereas the proliferative capacity of the responder T cells was the same than their controls.

We hypothesize that the inappropriate Type I IFN activation could contribute with the alteration in the suppressive function of Treg in individuals with T21, and this could explain the increased risk of leukemia and autoimmune disorders, as well as many developmental abnormalities also observed in interferonopathies.

Keywords: Trisomy 21, Regulatory T cells, Type I Interferon Signaling, Suppressive Function

(643) **EVALUATION OF THE EFFECTS OF SKIN ULTRAVIOLET LIGHT EXPOSURE ON PNEUMOCOCCAL VACCINATION EFFECTIVENESS**

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Cutaneous exposure to UV radiation (UVr) promotes well-known detrimental effects on health, as skin cancer development and specific immunosuppression. However, the impact of this immunosuppression on human vaccination has been poorly studied.

Previously, we have reported that a single high UV dose (shUVd - 400 mJ/cm^2) promotes skin inflammation and decreases CHS reaction. In contrast, repetitive low UV doses (rlUVd - 4 consecutive days, 20 mJ/cm^2) do not induce inflammation and increase CHS.

The aim of the present work was to study the effect of cutaneous exposure to shUVd and rlUVd on the effectiveness of a non-conjugated pneumococcal vaccine and on B-1 cells expansion.