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ANAIS DA XVIII EXPOPPGIM 2018
I Simpósio Norte-Nordeste em Imunologia

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SUMÁRIO

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Apresentação

O Programa de Pós-graduação em Imunologia (PPGIm) há vinte e nove anos, vem formando recursos humanos de excelência, capacitados para as atividades de ensino e pesquisa em Imunologia e áreas correlatas. O PPGIm tem realizado reuniões científicas anuais visando difusão do conhecimento científico e integração acadêmica com a graduação e a pós-graduação da UFBA e de outras IES.

A ExpoPPGIm, Reunião Anual do Programa, já se tornou um evento tradicional que acontece anualmente desde 2000. Essa reunião tornou-se um fórum de integração de profissionais, pesquisadores e jovens cientistas, alunos de graduação e pós-graduação da UFBA e de outras IES do Estado da Bahia e do Brasil com interesse no amplo domínio da Imunologia.

Neste sentido, o objetivo da ExpoPPGIm é divulgar o conhecimento científico em Imunologia e áreas correlatas, gerado localmente na Bahia, e agora, ampliando para o Norte-Nordeste com o I Simpósio Norte-Nordeste em Imunologia, tendo como público alvo graduados e estudantes de pós-graduação, pesquisadores da região e profissionais da área. Nesta XVIII Edição da ExpoPPGIm, tivemos conferências de pesquisadores do Programa, sessão de jovens cientistas, palestrantes representantes de Pernambuco, Paraíba, Pará, Sergipe, Maranhão, dentre outros Estados. Além disso, no primeiro dia do evento, contamos com a presença ilustre do Prof. Abul Abbas que ministrou um curso de imunologia básica, cujas sessões foram combinadas com palestrantes locais, apresentando seus dados em uma ótica translacional. Tivemos duas sessões de pôsteres, comunicações orais dos melhores trabalhos, incluindo a 3ª. versão do Prêmio Lain Carlos Pontes de Carvalho e a premiação do *Life-achievement award*, implementada em nosso primeiro simpósio regional.

Neste documento, sumarizamos a produção científica gerada para o I Simpósio Norte-Nordeste em Imunologia & XVIII ExpoPPGIm que teve como tema em 2018 "*Basic and Translational Immunology*". Assim, pretendemos disseminar a Imunologia, divulgar as idéias e projetos em curso desenvolvidos por docentes e discentes de nosso Programa, bem como, ampliar novas perspectivas, resgatando nossa história e instigando nossa evolução.

Saudações acadêmicas,

Camila A Figueiredo
Coordenadora do PPGIm/ICS/UFBA

LINHA 01:

IMMUNOLOGICAL FACTORS ASSOCIATED WITH DIABETES MELLITUS TYPE I: CELLULAR MECHANISMS

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Introduction: The type I diabetes mellitus (T1DM) is presented as an organ-specific autoimmune disease mediated by cells. The aim of this study is to describe the cellular mechanisms associated with the pathogenesis of T1D. **Methods and Results:** Data were collected from the literature using electronic databases PUBMED, Scientific Electronic Library Online (SciELO), Virtual Library on Health (BVS). The findings show that the main factors involved include cellular mechanisms triggered by CD4 + and CD8 + along the surface molecules of the Major Histocompatibility Complex (MHC) class I and II, with local production of cytokines such as Interleukin (IL-1) and Tumor Necrosis Factor (TNF). The genetic susceptibility is associated with changes in several genes, including the human leukocyte antigen (HLA), the protein associated to the cytotoxic T lymphocyte (CTLA-4), Protein Tyrosine Phosphatase (PTPN22), and MHC class II molecule**. Conclusion:** Environmental factors such as viral infection by Coxsackie B4 assigned to appear to play a role. So it turns out that there is in the literature a multitude of factors that contribute to the onset of DM1, certifying the need for development of more studies on this topic, for both this study aims to contribute by adding information to the theme of scientific knowledge together.

Keywords: Diabetes Mellitus Type I, Autoimmune disease and Cellular mechanisms.

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BIOMARKERS IN SEPSIS: AN OVERVIEW

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Introduction: sepsis is defined as a life-threatening organ dysfunction that is caused by a dysregulated host response to infection. Of note, although infection is the triggering event in this definition of sepsis, the aberrant immune response often remains after successful treatment of the infection. Sepsis clearly imposes a substantial global burden in terms of morbidity and mortality. Traditionally, diagnosis was based on presence of two or more positive SIRS criteria due to infection. However, recently published sepsis-3 criteria put more emphasis on organ dysfunction caused by infection in the definition of sepsis. Regardless of this, no gold standard for diagnosis exist, and clinicians still rely on a number of traditional and novel biomarkers to discriminate between patients with and without infection, as the cause of deterioration,and can diminish improper use of antibiotics and could be used for antibiotic stewardship**. Methods and Results:** In this narrative review studies were identified by searching PubMed, Web of Science, Science Direct, Scopus and Nature for English language articles published within the last years (January 2014 to July 2018) using the following keywords: sepsis OR sepsis syndrome AND biomarkers. The two authors critically reviewed the most relevant studies and found supplementary studies in the reference list of selected studies. The ability of biomarkers to identify the presence and severity of sepsis has generally been limited. Many biomarkers based on the magnitude of the inflammatory response, such as C-Reative Protein, IL6, IL10, CCL2, CXCL10 and HMGB1, have shown good correlation with the severity of sepsis and clinical outcome in population-based studies, but have proven less useful for individual patients, in large part because of the lack of specificity of the biomarkers and the commonality of the early inflammatory response. Our ability to distinguish sepsis from non-infectious critical illness and to prognosticate outcome is very limited. The one exception is in the use of procalcitonin to distinguish sepsis from non-infectious critical illness and to guide the use of antibiotic therapy. Two recent large meta-analyses of data from patients with respiratory infections showed that procalcitonin to guide antibiotic treatment in patients with respiratory infections was not associated with higher mortality rates or treatment failure. Serum levels of soluble triggering receptor expressed on myeloid cells 1 (sTREM1), soluble CD14, Macrophage Migration Inhibitory Factor (MIF), facell-surface CD64 (immunoglobulin G (IgG), Fc receptor in neutrophils are also potential biomarkers of sepsis. **Conclusion:** Biomarker research has thus far focused on discriminating between infectious and non-infectious causes of critical illness, and on sepsis prognosis. Future biomarker research should focus on the stratification of patients into more homogeneous subgroups on the basis of their pathophysiology, the identification of those who might benefit from a specific intervention and the validation of biomarkers that enable monitoring of the effects of targeted therapies.

Support: NOT FINANCED

Keywords: Sepsis, Biomarkers in sepsis, sepsis syndrome

TRICHODERMA ASPERELLOIDES SPORES DOWNREGULATE DECTIN2 AND TLR2 RECEPTORS OF MICE NEUTROPHILS

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Introduction: The intensive use of pesticides to control biological plagues has promoted several human health problems. Indeed, previous studies have demonstrated an association between pesticide exposures and human respiratory diseases.Among them, we highlight biocontrol agents derived from the fungi genus *Trichoderma*, which have been documented in limiting the growth of other phytopathogenic fungus in the roots and leaves of several plant species. An important member of this genus is *Trichoderma asperelloides*, whose biocontrol agents have been used to promote plant growth while also treating soil diseases caused by microorganisms in both greenhouses and outdoor crops. To evaluate the safety of fungal biological agents for human health, tests to detect potentially adverse effects, such as allergenicity, toxicity, infectivity and pathogenicity, are crucial. In addition, identifying possible immunomodulating properties of fungal biocontrol agents merits further investigation. Thus, the aim of this study was to evaluate the effects of *T. asperelloides* spores in order to elucidate the cellular and molecular mechanism of this interaction, as a model to understand possible in vivo effects of this fungus. **Methods and Results:** For this, mice were exposed to a fungal spore suspension through-intraperitoneal injection, euthanized and cells from the peritoneal cavity were collected for functional and phenotypic analysis, throughout analysis of membrane receptors gene expression. Our analyses showed that phagocytes exposed to fungal spores had reduced had reduced expression of pattern recognition receptors, such as TLR2 and dectin-2, all involved in the first line of defense against clinically important yeasts. Our data could infer that *T. asperelloides* spores may confer susceptibility to infection. **Conclusion:** Our analyses showed that phagocytes exposed to fungal spores had reduced had reduced expression of pattern recognition receptors, such as TLR2 and dectin-2, all involved in the first line of defense against clinically important yeasts. Our data could infer that *T. asperelloides* spores may confer susceptibility to infection.

Support: FAPESB

Keywords: biocontrol agent, fungal, PRRs.

LINHA 02:

EVALUATION OF SPECIFIC IMMUNE RESPONSES BY USING THE ADJUVANT EFFECT OF α-TOCOPHEROL, IN THE ACUTE AND CHRONIC PHASES OF *Trypanosoma cruzi* INFECTION

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Introduction: *Trypanosoma cruzi* infection triggers several reactions that culminate in recognition of the parasite and the composition of an innate or adaptive immune response. In an intermediate and late stage of the acute phase, CD4 and CD8 T lymphocytes may act to control parasitemia, parasite replication and parasite elimination in tissues. Vitamin E is a powerful antioxidant, with α-tocopherol being its most active isomer. Vitamin E injection has been shown to increase lymphocyte proliferation as well as the cytotoxic activity of NK cells. **Objectives:** To verify if after treatment with α-tocopherol there is alteration for pro-inflammatory or specific immune responses can help to eliminate *T. cruzi,* during the acute and chronic phase of the infection. **Methods and Results:** Female C57BL/6 mice were used and divided into the following groups: I-Intact control, II-treated with α-tocopherol (α-), III-treated with α- + *T.cruzi* antigens (α+TcAgs), III- treated with Alumen +TcAgs, IV- treated only withTcAgs. Mice were then immunized for four weeks (1 dose per week). After immunizations, half of the animals in the groups were infected with 50 trypomastigote forms of *T. cruzi* Tulahuen strain. Spleen cells from the experimental groups were evaluated by Flow Cytometry (FACS) using markers for CD4, CD8, NK, NKT and production of INF-γ was evaluated. Mice were bled, and specific *T. cruzi* anti-IgG profile was evaluated through ELISA, at three different time-points. α+TcAgs group had a lower parasitemia during the infection. Infected and immunized groups most importantly increased NK, NKT and TCD8 and TCD4 cells, when compared to infected control mice. Higher production of INF-γ was found in NK, NKT, CD8 as well in CD4+ T cells in α+TcAgs infected groups, when compared to the infected controls. Of note, only α (alone) or α+TcAgs groups presented higher interferon production for NKT cells (without stimulation in culture); when groups were compared to the infected unimmunized controls. **Conclusion:** α−Tocopherol has been shown to be a powerful adjuvant to induce a protective response to infections. Our next proposition is to verify the vaccinal protective effect of α+TcAgs, by monitoring the chronic phase of infection, upon re-vaccination of infected mice.

Support: PAPES / CNPq proc(407752/2012-9). and A.C.O.S has a FAPESB fellowship.

Key words: *T.cruzi,* vaccination, α-tocopherol, adjuvant effect.

IMMUNOBIOLOGICAL ASPECTS OF MESENCHYMAL STEM CELLS IN MURINE MODEL OF WOUND HEALING

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Introduction: Chronic leg ulcers (CLU) are very common with an estimated prevalence of 0.6 to 5% among patients over 65 years of age. CLUs are recalcitrant, cause a low quality of life and often lead to lower extremity amputation, representing both a significant health risk and a large economic burden. Adipose derived-mesenchymal stromal cells (Ad-MSC) are a potential alternative for treatment of CLUs. These cells secrete cytokines, growth factors, and bioactive molecules responsible for the effects of skin repair and regeneration. However, it has been reported that MSCs derived from patients with chronic inflammatory diseases have impaired angiogenic, proliferative and migratory capacity, and secrete less growth factors. Because there is a paucity of recent reports about Ad-MSC derived from sickle cell disease patients and its potential application for treatment of CLUs, we undertook this study to evaluate the imunobiological and regenerative mechanisms of the mesenchymal stem cells from sickle cell disease patients in a murine model of excisional wound healing. **Materials and Methods**: MSC were isolated from lipoaspirate samples, characterized (flow cytometry) and assayed for multilineage and immunomodulation potential (*in vitro*). Full skin thickness excisional wounds were created on the dorsum of the C57/Bl6 mice. Wound closure was monitored after surgery and healing rate was calculated based on wound area relative to the original size. Results: MSCs from SCD patients maintained the replicative capacity without significant loss of their specific biomolecular characteristics, multi-differentiation potential. Standardization experiments of the skin excisional wound model are in progress. **Conclusion:** These data demonstrate the feasibility of expanding adipose tissue-derived MSCs from SCD patients and that these cells display immnobiological properties that are important for cell therapy of chronic leg ulcers.
Support: FAPESB, CNPq and PIBIC-UFBA.

Keywords: MSC, chronic ulcers, cell therapy.

PRODUCTION OF CYTOKINES BY HUMAN PERIPHERAL BLOOD MONONUCLEAR CELLS STIMULATED WITH SYNTHETIC PEPTIDES OF *Porphyromonas gingivalis*

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Introduction: Chronic periodontitis is a progressive inflammation of the periodontal tissues, whose pathogenesis is related to a dysbiotic subgengival biofilm. Among the microorganisms involved, *Porphyromonas gingivalis* (Pg) is a keystone pathogen in the human oral dysbiosis. This pathogen present virulence factors, such as Lys-gingipain (Kgp), which contribute to the permanence and dissemination of the bacteria in its host. Kgp is involved in the host-bacterial interaction through the production of cytokines. However, the specific mechanisms of this interaction are not elucidated yet. Thus, the present study aimed to evaluate the *in vitro* production of IFN-γ, IL-1β and IL-6 in response to the antigenic stimulation with immunoreactive Kgp synthetic peptides. **Methods and Results:** The Kgp synthetic peptides were obtained by *in silico* study of the protein sequence; in which 16 peptide sequences from Kgp were obtained, nine of them were chemically synthesized and three (Kgp 12, 17 and 18) were selected according to their IgG immunoreactivity in sera samples of individuals with chronic periodontitis (CP) and without periodontitis (WP). Peripheral blood mononuclear cells (PBMC) from subjects with CP and WP were stimulated with Kgp 12, 17 and 18 peptides, Pg total extract and HmuY recombinant protein of Pg. The Kgp peptides induced low concentrations of IFN-γ in PBMC cultures, which is in accordance with the extracellular behavior of the pathogen. Even low, Kgp12 induced higher production of IFN-γ in WP individuals when compared to CP ones. When compared to the other stimuli, Kgp12 also induced high production of IL-6 and IL-1β, which was similar to the Pokeweed mitogen. **Conclusion:** The analysed peptides, especially the Kgp12 synthetic peptide (IEDB epitope ID 763561), may be useful tools in evaluating the host-pathogen interaction in human cells, since it is more economically viable using the synthetic peptide rather than the Kgp recombinant protein. In addition, using a specific peptide like Kgp12 decreases the risk of cross reactivity in the opposite way of using the total extract of the microorganism.
Support: FAPESB, FAPEX, LABIMUNO (ICS - UFBA), PPGIm (ICS - UFBA), NUPPIIM (UEFS), NECBAO (EBMSP).

Keywords: periodontitis, Lys-gingipain, IFN-γ, IL-6, IL-1β, immunogenic synthetic peptides.

THE USE OF *Bacillus Calmette-Guérin* (BCG) IN IMMUNOMODULATION OF EXPERIMENTAL MELANOMA IN C57BL/6 MICE

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Introduction: BCG, an attenuated *Mycobacterium bovis* vaccine-strain, induces a non-specific immune response that can be essential for effective antitumoral activity. As BCG is a promising immunostimulant, we aimed to test BCG as an adjuvant to anti-melanoma therapy. **Methods and Results:** Tumor growth and survival were evaluated in C57BL/6 mice grafted with B16F0 melanoma tumor cells in the pinna of the ear, followed by the localized injection of BCG *in vivo*. Animals received $5x10^4$ of B16F0 via intra-ear route, while BCG was injected at $1.2x10^7$ of vehicle *in situ* 10 days after tumor injection. Additional groups received exclusively tumor cells or BCG, and a non-manipulated control group was also included. Tumor growth and animal mortality were monitored daily. The inoculation of BCG *in situ* resulted in a remarkable reduction in tumor growth compared to mice that received only tumor cells (B16F0). Earlier mortality was observed in the B16F0 group compared to inoculated mice that also received BCG (B16F0+BCG) ($p < 0.0001$; Log-Rank test), in addition to increased survival rates in these animals. Statistically significant differences in tumor size were observed between the B16F0+BCG and B16F0 groups on the 18th day after tumor injection ($p=0.0298$, Mann-Whitney). Increases in splenic dendritic cells (DCs) were seen on day 18 in the B16F0+BCG mice compared to those receiving B16F0 alone ($p=0.0286$; Mann-Whitney test). In addition, CD8+ T cells were also increased in the B16F0+BCG mice compared to the other groups ($p=0.0348$; Kruskal-Wallis test). Decreased numbers of Treg cells and the maintenance of MDSC cells were observed in the B16F0+BCG mice compared to the B16F0 group. FACS evaluation of cytokine production revealed decreased IL-10 and TNF-α production, in addition to the maintenance of INF-γ production by CD4 + and CD8 + T splenocytes, in the B16F0+BCG group compared to B16F0 mice. BCG was found to limit B16F0 melanoma tumor development and significantly increase survival rate in C57BL/6 mice. In addition, treatment with BCG resulted in increased numbers of splenic dendritics and CD8 + T lymphocyte cell populations. **Conclusion:** Therefore, BCG (or some of its products) presents potential to induce protection against tumor cells, and is suitable for use in studying mechanisms involved in the control of melanoma.

Supported by PAPES (407752/2012-9)-CNPq.

Keywords: Experimental Melanoma, BCG, Adjuvant therapy, immunostimulation.

IMMUNOSUPRESSIVE ABILITIES OF MESENCHYMAL STEM CELLS ARE NOT DEFECTIVE IN SICKLE CELL DISEASE PATIENTS WITH OSTEONECROSIS

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Introduction: Osteonecrosis is a chronic, painful and severe complication in sickle cell disease (SCD). Osteonecrosis results from microcirculatory obstruction by sickled erythrocytes and leucocytes leading to ischemic-reperfusion injury of bone and necrosis. Therapy with Mesenchymal Stem Cells (MSC) induce bone formation and has been the best alternative to treat osteonecrosis in SCD patients. MSC secretion of cytokines and growth factors have unique immunomodulatory properties and is very useful for bone repair caused by chronic damage. Here we tested whether bone marrow (BM)-derived MSCs from SCD patients with ON have immunosuppressive effects on T cell proliferation and their profile of cytokines. **Methods:** MSC were isolated from bone marrow aspirates (BM), cultivated and characterized. Immunomodulation potency assay of activated T-cells was tested during co-cultivation of MSC with PBMC isolated from control or SCD patients with osteonecrosis (SCD/ON). MSC-induced suppression of CD4 T-cell proliferation was measured with CFSE staining. Cytokines in MSC and PBMC co-cultures were measured with CBA Th1/Th2/Th17 Kit, according to the manufacturer's protocol. MSC from SCD patients showed replicative capacity, typical surface markers, multi-differentiation potential, and osteogenic differentiation activities MSCs also demonstrated strong potential for immunomodulation by suppressing lymphocyte proliferation in a dose-dependent manner from both control and SCD/ON patients. Pro-inflammatory cytokine expression in co-culture supernatant did not differ between control and SCD/ON PBMCs, although they differ between non stimulated, activated and co-cultured with MSCs PBMCs. **Conclusion:** These results demonstrate the feasibility of expanding BM-derived MSCs from SCD patients and their immunomodulatory capacity, suppressing proliferation of third-party and autologous T cells with similar expression of pro-inflammatory cytokines in co-culture supernatant.
Support: FAPESB

Keywords: immunomodulation, sickle cell disease, co-culture

EVALUATION OF THE OSTEOGENIC POTENTIAL OF CD271^{+}CD45^{low} MUTLPOTENTIAL STROMAL CELLS FROM BONE MARROW IN PATIENTS WITH OSTEONECROSIS

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Introduction: Aspiration of iliac crest bone marrow (BM) remains the most frequent technique used in harvesting multipotential stromal cells (MSCs) for bone regeneration. CD271, also known as LNGFR (low affinity factor receptor of nerve growth or p75NTR) belongs to the superfamily of necrosis factor
tumor. This cell surface marker potentially defines a subpopulation of MSC precursors that displayed a higher efficiency of proliferation and trilineage differentiation and can be used for enrichment of non-hematopoietic stem cells from bone marrow aspirate, representing a promising therapeutic strategy for bone defects. **Methods and Results:** Approval for these studies was obtained from the UFBA ethics committee, iliac crest bone marrow aspirate was obtained from 9 patients with osteonecrosis. A 50 µl volume of whole bone marrow and $5x10^5$ mononuclear cells isolated from the BM aspirate on a Ficoll density gradient was stained for couting CD271^{+} CD45^{low} cells using flow citometry. The colony forming unit fibroblast (CFU-F) assay was used to the determination of the quality of bone marrow samples and each colony was defined as having at least 50 cells. With respect to the number of couting CD271^{+}CD45^{low} cells in a bone marrow concentration was higher compared with BM aspirates. **Conclusion:** Bone marrow samples contain progenitor stromal cells that are potentially useful with therapeutic strategy for bone regeneration. In this work, we try to shown that a cytometric assay can be used to evalueted the potential or quality of the bone marrow sample applied in clinical settings.
Support: CNPq.

Keywords: bone marrow aspirate, multipotential stromal cells, osteonecrosis.

MYELOID DERIVED SUPPRESSOR CELLS PROMOTE IMMUNOMODULATORY EFFECTS IN EXPERIMENTAL CHAGAS´ DISEASE CARDIOMYOPATHY

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INTRODUCTION: Chagas disease is one of the most serious parasitic diseases in the world. Chronic Chagas' heart disease is the final common pathway of in distended heart disease. Due the absence of effective therapies capable of directly reverting the pathophysiological disease demonstrates urgent necessity of new therapeutic approaches. The present study evaluated the therapeutic effects of Myeloid derived suppressor cells (MDSC-CD11b/GR1$^+$) in the experimental model of chronic Chagas cardiomyopathy**. METHODS AND RESULTS:** C57BL/6 mice were infected with 1000 trypomastigotes of T. cruzi (Colombian strain) for six months, then were treated with CD11b/GR1+ cells sorted from bone marrow of GFP mice. The treated group received 2 intravenous injections of MDSC (1x10^6 cells/injection), with the interval of 1 month each dose. All animals were euthanized under anesthesia following 2 months of treatment for morphometric analyzes of the heart, as well as the assessment of inflammatory cytokines expression by qRT-PCR and Elisa in the serum. Mouse heart sections from group treated with MDSC were evaluated by immunofluorescence to observe the presence of GFP$^+$ cells in the myocardium. After 24 hours of injection, GFP$^+$ cells were visualized in the heart. The morphometric analyzes in the heart of animals treated with MDSC reveal a significantly reduced number of inflammatory cells when compared to Chagas animals treated with saline. In addition, the inflammatory cytokines expression in the heart was significantly reduced in the group that was treated with MDSC as well as in the serum. **CONCLUSION:** Thus, these data suggest that treatment with purified Myeloid derived suppressor cells from bone marrow have therapeutic effects in relation to its ability to reduce inflammation in the heart of mice chronically infected with T. cruzi. Additionally, this therapeutic approach modulated the expression of inflammatory cytokines commonly expressed in Chagas disease cardiomyopathy leading to an overall improvement in the cardiovascular health in this model.

KEYWORDS: Chagas' cardiomyopathy, cell therapy, Myeloid derived suppressor cells

Fonte de financiamento: Cnpq

ASSESSING PROTEOLYTIC STABILITY OF *Blomia tropicalis* ALLERGENIC PROTEINS AND HYBRID PROTEINS DERIVED FROM THESE ALLERGENS BY DEGRADOME ASSAY

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Introduction: The link between weak capacity of T cell priming of antigens *in vivo* and their high susceptibility to endolysosomal proteases *in vitro* has been used to provide information on antigen immunogenicity. Although Blo t 5 and Blo t 21 are well-known major allergens, little or none is known about their immunogenic properties and T cell epitopes. Thus, we aimed at predicting the immunogenicity and peptide patterns of two variants of Blo t 5, Blo t 21 and two hybrid proteins (BTH1 and BTH2) derived from these allergens. **Methods and Results:** Endolysosomal degradation and peptide clusters were simulated using microsomes isolated from the dendritic cell line JAWS II. After freezing/thawing cycles, the microsomal fractions were incubated with the proteins during certain time points at 37°C. Degradation kinetics and peptide patterns were evaluated by SDS-PAGE 15% and tandem mass spectrometry. SDS-PAGE analysis revealed that rBlo t 5_{long} was completely degraded after 24 hours while rBlo t 5_{short} was only completely degraded after 48 h, indicating an increased resistance of rBlo t 5_{short} towards endolysosomal degradation. BTH1's resistance towards endolysosomal degradation was visibly higher than that of rBlo t 21, which was also not completely degraded after 48h. On the other hand, BTH2 showed similar proteolytic stability when compared to rBlo t 5_{short}, but higher than rBlo t 5_{long}. Through densitometric evaluation we calculated half-lives of 4.9 h, 8.7 h, 17.4 h, 39.4 h and 8.5 h for rBlo t 5_{long}, rBlo t 5_{short}, rBlo t 21, BTH1 and BTH2, respectively. Tandem mass spectrometry analysis showed differences in the peptides clusters generated by proteolysis of the hybrid proteins when compared to the parental allergens. The predominant peptide fragments of BTH1 were detected amongst the four most predominant peptide fragments of rBlo t 5. Two out of these four identified peptide clusters comprised the previously-reported T cell epitopes of Blo t 5. The hypoallergenic hybrid BTH2 displayed peptide fragments that are shared with both parental allergens in all time points. Our data suggest that the N-terminus region of the proteins seem to be initially cleaved, leading to the notion of a potential cathepsin cleavage site at the amino acid residues 20-23 (LYL) in the hybrid proteins. **Conclusion:** The shortening of Blo t 5 led to a reduced susceptibility to endolysosomal proteolysis. Since the stronger resistance of BTH1 in comparison with the parental allergens might be excessive, which can lead to inefficient antigen presentation, we conclude that the hypoallergenic hybrid BTH2, for its more diverse peptide pattern, seemed to be a better option for allergen-specific immunotherapy. Nevertheless, more studies are required, using the new identified peptide fragments in peripheral blood mononuclear cells culture and murine *in vivo* models, to confirm our predictions.

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Keywords: Blo t 5, Blo t 21, hypoallergen, T cell epitopes, immunogenicity.

HIGH LEVELS OF ANTI-CARDIOLIPIN ANTIBODIES IN PATIENTS WITH BORDERLINE LEPROMATOUS AND LEPROMATOUS LEPROSY

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Introduction: Antiphospholipid antibodies (aPL) have been reported not only in autoimmune disorders but also in various infectious diseases, such as leprosy. The most commonly discussed aPL antibodies is the anticardiolipin antibody (aCL). Interestingly, aCL are often present in leprosy, although they do not appear to be correlated with thromboembolic events, possibly reflecting a distinct pathophysiological significance. The aim of this study was to evaluate aCL levels in leprosy patients and its association with clinical profile of the disease. **Methods and results:** Samples of 5 mL of peripheral blood were collected from leprosy patients (N=56), which were classified as indeterminate (IL, n=6), tuberculóide (TT, n=11), borderline tuberculoid/borderline-bordeline (BT/BB, n=7), borderline lepromatous (BL , n=21) and lepromatous (LL, n=11) and endemic controls (n=13) without any signs and symptoms of leprosy. aCL levels were measured using Enzyme-Linked Immunosorbent Assay (ELISA) technique. Non-parametric tests of Mann-Whitney and Kruskal-Wallis were used for comparison between groups. The Spearman test was applied to correlate clinical data and immunoglobulin levels. Levels of IgG aCL were significantly higher in BL or LL compared with other patient groups (IL, TT, BT/BB) and endemic controls ($p<0.0001$). In contrast, no significant differences were observed between the BL and LL groups ($p=0.271$). The level of IgG aCL is higher than those presented by IgM ($p <0.0001$) and the demonstrated result is independent of gender, bacillary index and operational classification. Multibacillary patients have a greater quantitative of cutaneous lesions (median= 6; 1-100) than paucibacillary lesions (median=1;1-5; $p <0.0009$). Although there was no difference in IgM clearance between clinical forms ($p=0.224$), the increase in IgM aCL production had a positive correlation with bacillary index ($p = 0.0016$, $r = 0.41$) and the number of cutaneous lesions in multibacillary patients ($p < 0.0001$; $r = 0.58$). **Conclusion:** The results indicate that high levels of IgG aCL may be useful for detect BL or LL patients and, therefore, may be useful when making therapeutic decisions. The increased IgM aCL level indicates a possible worse prognosis in leprosy patients.

Key-words: Leprosy, clinical forms, antibody, anticardiolipin.

Financial support: FAPESB, CNPq.

DEVELOPMENT OF A NANOPARTICLE SYSTEM AND EVALUATION OF ITS ADJUVANT POTENTIAL ON LEISHMANIA NUCLEOSSOMAL HISTONES

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INTRODUCTION: Leishmaniasis is an endemic disease in tropical and sub-tropical countries that has an important impact on public health; estimates attribute 50,000 annual deaths and 3.3 million DALYs. Treatments for leishmaniasis are few, toxic, and expensive, furthermore, drug resistance is on the rise. Thus, vaccination would be the most cost-effective approach. Previous studies demonstrated that nuclessomal histones antigens delivered as DNA formulations induced partial protection in experimental infections. It's known that nanoencapsulated antigens can induce localized and long lasting immune responses. Proteins formulated in nanoparticles are better presented for dendritic cells (DC), which are the key cells for the development of a protective immune response against leishmaniasis. Our working hypothesis is that nuclessomal histones encapsulated in solid lipid nanoparticles (SLN) will promote a better activation of DCs, inducing a Th1 immune response. **METHODS AND RESULTS**: Anionic and cationic SLN were prepared by the double emulsion method. Precirol ATO 5 was used as a lipid, and chitosan was added in the extern aqueous fase to obtain cationic SLN. The particles were analysed by size, polydispersity index (PdI) and zeta potential by dynamic light scattering. A total of 8 lots were prepared to obtain standardized anionic SLN, resulting in a formulation with a mean dimeter of 194.4 nm, PdI of 0.16 and zeta potential of -32.9 mV. For cationic SLN, 5 lots were prepared, resulting in a formulation with a mean diameter of 257.2 nm, PdI of 0.43 and zeta potential of +51.9 mV. The particles stability was evaluated during 60 days after formulation and cationic SLN reveled to be more stable than the anionic. After that, BSA-FITC (2 mg) was formulated as a model protein using the established conditions. Next, SLN uptake was evaluated using bone marrow derived macrophages and confocal microscopy. After 4 hours' of incubation, it was possible to observe that both SLN were efficiently phagocytosed by the macrophages. **CONCLUSION**: It was possible to produce anionic and cationic SLN. These nanoparticles were stable after 60 days at 4 °C. Preliminary results show that SLNs are efficiently delivered for macrophages. The next step is to evaluate the SLN adjuvant effect on bone marrow dendritic cells by flow cytometry and confocal microscopy using albumin as a model protein, completing the standardization stage and setting the stage to formulate the nucleossomal histones.

Financial Support: IGM, CNPq.

Keywords: leishmaniasis, vaccine, delivery, nucleossomal histones.

DIFFERENTIAL GENE EXPRESSION PROFILES OF INDIVIDUALS WITH ACTIVE AND LATENT TUBERCULOSIS, VACCINATED OR NOT WITH BACILLUS CALMETTE-GUÉRIN (BCG)

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Introduction: Tuberculosis (TB) presents a clinical spectrum of infection-disease that is poorly understood. The published profiles of gene expression in different phases of the infection-disease were studied to search for biomarkers that may help anticipate active disease onset. Transcriptional signatures putatively capable of predicting the evolution from the latent to the active form of disease have been described in different studies. However, these studies have not taken into account vaccination with BCG, that is widely used against TB and has been demonstrated to have pleiotropic effects on the body. In this work we performed a meta-analysis of published gene expression profiles of individuals with active TB, latent infection and healthy controls, stratified by BCG vaccination status. **Methods and Results:** Transcriptome data were obtained from the public repository Gene Expression Omnibus (GEO), from three datasets that evaluated whole blood samples of individuals with established BCG vaccination status that presented active or latent TB, as well as uninfected controls. Data were normalized and corrected to remove batch effects. Canonical pathways, molecular and cellular functions were evaluated using the Ingenuity Pathway Analysis (IPA) tool. Seven genes were modulated in the vaccinated group when comparing active TB, latent disease and controls, while in the unvaccinated group the same comparison yielded one hundred modulated genes. It is possible to recognize genes associated with cell death and survival, cellular movement and organization, as well as molecular transport, upregulated among active TB patients in both vaccinated and unvaccinated strata. While among vaccinated individuals the active TB patients have diminished expression of genes related with lipid metabolism, among unvaccinated subjects there is downmodulation of genes related to cell cycle, cell-to-cell signalling, cellular growth and proliferation. **Conclusion:** We found a distinct profile of differentially expressed genes depending on the vaccination status, when comparing individuals with active TB, with latently infected and uninfected controls. Early-life vaccination with BCG can have lasting and pleiotropic effects that modulate the regulation of processes involved in TB infection and disease, with especial regard to important pathways involved in mycobacterial metabolism.

Support: FAPESB, CNPq and Fiocruz

Keywords: *Mycobacterium tuberculosis*, transcriptomics, systems biology, vaccine, pathogenesis.

LINHA 03:

JM-20 AND AGATISFLAVONE INHIBIT THE ALPHA-SYNUCLEIN TOXICITY LINKED TO PARKINSON'S DISEASE.

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Introduction: Parkinson's disease (PD) is one of the most prevalent neurodegenerative diseases. There is a hypothesis that the alpha synuclein (α-sin) aggregation generates the formation of neurotoxic protofibrils leading to the pathogenesis of this disease. Aminochrome induces the formation of neurotoxic protofibrils, dysfunction of altered protein degradation, mitochondrial dysfunction, generation of oxidative stress and neuroinflammation which are involved in the pathogenesis of PD. **Methods and Results:** In this study, SH-SY5Y cells were cultured in DMEM-HAMF12 medium and maintained under optimum conditions. Cells were maintained with the flavonoid agatisflavone at concentrations of 0.1-50 μM for 24 h and / or with 10 μM aminochrome for 24 h. The neuroprotective activity was performed by the calcein AM test and the analysis of mitochondrial dysfunction was performed by acridine orange dyes, lysossensor and JC1. Microglial cells were maintained with agatisflavone at concentrations of 0.1 and 1 μM for 12 or 24 h and / or with alpha-sin fibril at 2.5 and 5 μM for 12 h and microglial activation was assessed by immunocytochemical labeling for microglia-specific IBA-1 protein and nitric oxide measurement. Alfa-sin at the concentration of 120 μM with agatisflavone and JM20 at concentrations of 0.1 and 1 μM was kept under stirring for 120 h at 37 ° C. Inhibition of α-sin aggregation was assessed using the dye Thioflavine (ThT) and Electron Microscopy. **Results and Discussion:** We have shown that the flavonoid agatisflavone does not present a cytotoxic profile in cells exposed to concentrations of 0.1-50 μM for 24 h. In addition, the flavonoid agatisflavone at concentrations 0.1 and 1 μM protected the cells against aminochrome induced damage at 10 μM concentration for 24 h. In addition, we have shown that agatisflavone (0.1 and 1 μM, for 24 h) does not cause lysosomal dysfunction, characterized by increased red fluorescence when compared to control. (10 μM, for 24 h) induced loss of lysosomal acidity and agathisflavones (0.1 and 1 μM for 24 h) restored the acidification of this organelle and maintained membrane potential. In addition, agathisflavone (0.1 and 1 μM, for 12 and 24 h) was able to protect the microglial cells submitted to damage with fibrils. JM 20 was able to accelerate the formation of alpha-sin fibrils, thereby decreasing the availability of the intermediate fraction which are the oligomers which have the most neurotoxic effect. **Conclusion:** These results demonstrate the neuroprotective ability of agathisflavone and JM20 by pointing to these compounds as possible therapeutic agents for the treatment of Parkinson's Disease.

Support: FAPESB, CAPES, CNPq

Key words: Flavonoid, aminochrome, Microglia, Alpha-synuclein

RUTIN MODULATES THE MICROGLIAL RESPONSE TO LPS EXPOSURE AND THE EFFECTS OF MICROGLIA CONDITIONED MEDIUM IN PC12 CELLS

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Introduction: Several flavonoids, among them rutin, have an important influence on modulation of the microglial response and its released soluble factors. Our research group recently discovery that rutin modulates microglial/macrophage activation to a CD150/CD206 M2 phenotype. Microglia emerges as a central player in pathogenesis of neurodegenerative diseases associated with neuroinflammation, among them Parkinson's disease and Alzheimer's disease. Studies have demonstrated that these cells are capable of release factors that interfere in the biology of neurons in terms of cell differentiation and viability. **Objectives:** To study the effect of soluble factors released by microglial under inflammatory or regulatory immune response. **Methods and Results:** Primary cultures of microglia from P0-2 Wistar rats were treated with 0.1% DMSO (negative control) or LPS (1 μg/mL) and/ or rutin (0.5 and 1 μM). After 24 h treatment, the culture medium was replaced and collected 24 h for use as microglia conditioned medium (MCM). Modulation of cytokines and Neurotrophic was performed in microglia by qPCR. PC12 cells were treated for 24 h with the MCMs, followed by staining with Rosefeld`s technique and morphological analysis. Induction of autophagy was analyzed by Western Blot for LC3II and lysosomal function was analyzed by placement with acridine orange. It was observed that MCM derived from LPS treatment induced changes in PC12 cells morphology to a bipolar-like shape, cytoplasmic vacuolation and condensed nuclei that were not visualized in cells exposed to MCM derived from treatments with LPS + 1μM rutin. On the other hand, no changes were observed in terms of LC3-II expression and lysosomal acidification in PC12 cells under any MCM treatment conditions. Indeed, the qPCR results demonstrated that LPS increases level of TNF, IL-6 and NLRP3 mRNA, contrariwise rutin increases levels of GDNF and ARG mRNA. **Conclusion:** These results suggest that MCM from LPS treatments induces morphological changes in PC12 cells, that is inhibited by the modulatory effects of rutin in microglial cells. More studies should be performed to better characterize the morphogenic components of MCM and association of the effect with neuronal differentiation or distress.

Support: FAPESB, CAPES, CNPQ

Key-words: LPS, microgliosis, rutin, morphogensis, neuronal distress.

IMPLICATIONS OF SEXUAL HORMONES AND IL-10 IN THE SEX DIFFERENCES DURING THE CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Introduction: The Chronic Obstructive Pulmonary Disease (COPD) is a chronic lung disease which is characterized by limitation of the airflow and local inflammation, caused mainly by the long term exposure to the cigarette smoke. Several articles have shown that female patients present more comorbities, more dyspnea and develop severe emphysema even with less time as smoker than male patients. Some authors have described alterations in sexual hormone levels in COPD patients, but they have not evaluated the impact of these changes in immune system and in the disease. **Methods and Results:** The aim of the study was to evaluate whether patients with COPD have alterations in serum concentration of estradiol and testosterone, and whether the hormone levels were associated to inflammatory (IL-1β, IL-8, IL-6, IL-10, IL-12 and TNF) and prognosis markers of the disease. Thirty-nine patients (COPD) and the same number of healthy controls (CG, control group), which were pared by sex and age, were included in this study. Female patients presented worse clinical and functional parameters such as DTC6; dyspnea on the mMRC scale, BODE index, quality of life for AQ20, and predicted FEV1% than male patients. They also showed lower levels of IL10 than males. However, there were not differences in hormone levels between COPD and CG females. Nevertheless, COPD males exhibited higher levels of estradiol than CG males. Estradiol and testosterone serum concentrations correlated with several clinical and immunological markers. Results showed a positive correlation between testosterone and IL-10 levels. **Conclusion:** The sex differences observed in COPD could be related to the immunomodulatory effect of testosterone in the IL-10 production. More studies are necessary for the elucidation of the role of sex hormones in the regulation of inflammation during the COPD.

Keywords: COPD, cytokines, sex hormones and sex differences.

EVALUATION OF GASTROPARESIS IN HEMIPARKINSONIAN RATS.

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Introduction: In addition to motor problems, the quality of life of patients with Parkinson's disease (PD) is severely impaired by a variety of non-motor symptoms including gastrointestinal dysfunction. The Enteric Nervous System (ENS) is responsible for controlling intestinal motility and a typical feature of PD is constipation. The involvement of ENS and the gut has been shown to be important in the pathophysiology of PD. OBJECTIVES: To assess the change in intestinal transit in a 6 OHDA-induced PD model in rats. **Materials and methods:** Male Wistar rats (250-300 g, n = 6 animals per group) were anesthetized and submitted to unilateral intrastriatal injection of 6-OHDA (21 µg) or Saline (0.9%) (Control group). Animals were given carmin red 6% for evaluation of gastrointestinal motility. The fecal pellets were collected, counted and weighed every 3 hours, during 12 hours. Total fecal matter was dried overnight at 60 ° C and total moisture was analyzed. Animals were also submitted to behavioral tests (Open-field test, Cylinder test and Rotation test induced by apomorphine [3 mg/kg, i.p.]). **Results:** The 6-OHDA group showed decreased locomotor activity in the Open-field test (30.0 ± 5.1) compared to the control group (54.2 ± 2.9), also showing reduced performance on the cylinder test. In the rotational test, the 6-OHDA group increased the number of rotations in comparison with the control group ($p<0.05$). The animals in the 6OHDA group exhibited a significant decrease in fecal water content (22%), reduced fecal yield and delay in gastroesophageal estrus of approximately 5 h when compared to the control group. **Conclusion:** The results showed that the animals submitted to the 6OHDA lesion, in addition to presenting motor deficit, presented altered intestinal transit, with reduction of gastrointestinal motility, reduction of pellets and fecal moisture. These data suggest that this model is adequate to evaluate the participation of ENS in the pathophysiology of PD.

Support: FAPESP, CNPq and CAPES

Keywords: Enteric Nervous System, Parkinson's disease and Gastrointestinal motility

INVESTIGATION OF NEUROPROTECTIVE AND ANTI-INFLAMMATORY ACTIVITY OF APIGENIN *IN VITRO* MODELS OF NEUROINFLAMMATION

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Introduction: Alzheimer's Disease (AD) is characterized by accumulation of the β amyloid protein (Aβ) and increase of inflammatory response mediated by microglia and astrocytes, which once activated, release pro-inflammatory cytokines such as IL1β, resulting in neurodegeneration. This study evaluated the neuroprotective and anti-inflammatory potential of flavonoid apigenin *in vitro* models of neuroinflammation induced by LPS, IL1β or Aβ. **Methods and Results:** Co-cultures of neurons and glial cells were cultivated from the cortex of Wistar rats. Cells were exposed for 24 h to LPS (1µg/mL) or IL1β (10ng/mL) or for 4 h to oligomers Aβ (500 nM) and then treated with apigenin (1µM) for more 24 h. It was observed by Fluoro Jade B and caspase 3 immunostaining that apigenin was not neurotoxic and has a neuroprotector effect against inflammatory damage. The immunofluorescence analysis revealed that apigenin reduced microglial inflammatory activation and proliferation through decrease of staining for CD68 and BrdU markers, respectively, and preserved neuronal and astrocytic of cellular integrity, also modulating the microglial morphological pattern, determined by staining for βtubulin III, GFAP and Iba1 proteins, respectively. The immunomodulatory effect of apigenin, evaluated by qPCR demonstrated that apigenin did not induce changes on expression of IL-6, IL-1β and CCL5 and induced increase the expression of BDNF. IL-1β treatment induced increase in the levels of IL-1β, IL-6, and CCL5, and decrease the expression the IL10 and BDNF. However, association of apigenin to IL-β induced decrease in the expression of IL-6 and CCL5 and increase the expression of IL-10 and BDNF. **Conclusion:** These data suggest that apigenin presents neuroprotective and anti-inflammatory potential.

Support: CNPq, CAPES

Key words: Alzheimer Disease, Neuroinflammation, Neuroprotection, Anti-inflammatory, Flavonoids.

NOVEL BETULINIC ACID-CONTAINING RUTHENIUM COMPLEX: SYNTHESIS, CYTOTOXICITY AND IMMUNOMODULATORY ACTIVITY

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Introduction: Inflammatory responses are present in various physiological and pathological processes. In both cases, a certain degree of the phenomenon is essential for organ function, infection control and tissue remodeling. However, excessive inflammation can lead to degenerative, neoplastic and organ failure processes. Cancer is a multifactorial disease initiated by genetic mutations that cause a disruption in cell proliferation. Chemotherapy is one of the most important methods to treat the conditions; however, currently available drugs have limitations related to high toxicity and the development of resistance. Betulinic acid (BA) is a naturally occurring triterpenoid endowed with a number of biological properties, including cytotoxicity and immunomodulatory activity. Here we investigated the cytotoxicity and immunomodulatory activity of a novel ruthenium compound, denoted as [Ru(BA)(dppb)(4,4-Mebipy)]PF_6 (RuBA). **Methods and Results:** Initially, the cytotoxic activity towards tumor cell lines (HCT116, HepG2, K562 and MCF-7) and non-tumor cells (J774 and MRC5) was evaluated using the AlamarBlue assay. Then, the immunomodulatory activity was evaluated on J774 macrophages activated with IFN-γ and LPS through determination of nitric oxide (NO) production by Griess method. Finally, the effect of complex on lymphocyte proliferation was evaluated using splenocytes cultures stimulated with concanavalin A by assessment of ^{3}H-thymidine incorporation. The compound RuBA exhibited high cytotoxicity against tumor cells, showing IC_{50} values of 1.57 and 6.4 µM against the K562 and HCT116 cell line, respectively. Regarding, cytotoxicity against non-tumor cells, non-cytotoxicity effect was observed in the tested concentrations, showing a selectivity profile of the complex. When tested in macrophages cultures stimulated with IFN-γ and LPS, the complex significantly decreased NO production in a concentration dependent manner. Additionally, the complex also significantly inhibited the proliferation of activated lymphocytes. **Conclusion:** Our results reinforce the potential use of betulinic acid and its derivatives in the search for potent anticancer and immunomodulatory drugs.

Support: FAPESB and CNPq

Keywords: Betulinic acid derivative; Lymphocyte function; Macrophage activation; Ruthenium complex.

BETULINIC ACID DERIVATIVE BA5, ATTENUATES INFLAMMATION AND FIBROSIS IN EXPERIMENTAL CHRONIC CHAGAS DISEASE CARDIOMYOPATHY BY INDUCING IL-10 AND M2 POLARIZATION

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Introduction: Chagas disease is a zoonosis caused by the protozoan hemoflagellate *Trypanosoma cruzi*, which affects millions of people in Latin America. In Brazil and in many countries, the treatment of this disease is based on the use of benznidazole. Its use is associated with a number of side effects throughout the treatment and has a low cure rate in individuals with chronic disease. In this context, the development of new drugs for a proper chemotherapy of chronic Chagas' disease is necessary, especially in the cardiac form of the disease. Here we investigated the effects of BA5, an amide semi-synthetic derivative betulinic acid, in a model of chronic chagasic cardiomyopathy (CCC). **Methods and Results:** Mice chronically infected with *T. cruzi* were treated orally with BA5 (10 or 1 mg/Kg), three times per week, for two months. Then, subjected to evaluations of cardiac function, quantification of inflammation and fibrosis in the heart, serum cytokines by ELISA, and PCR analyzes to evaluate the modulation of gene expression in the heart and the parasite load on the spleen. BA5 treatment decreased inflammation and fibrosis in heart sections but did not improve exercise capacity or ameliorate cardiac electric disturbances in infected mice. Serum concentrations of TNF-α, IFN-γ and IL-1β, as well as cardiac gene expression of pro-inflammatory mediators, were reduced after BA5 treatment. In contrast, a significant increase in the anti-inflammatory cytokine IL-10 concentration was observed in BA5-treated mice in both tested doses compared to vehicle-treated mice. Moreover, polarization to anti-inflammatory/M2 macrophage phenotype was evidenced by a decrease in the expression of NOS2 and proinflammatory cytokines and the increase in M2 markers, such as Arg1 and CHI3 in mice treated with BA5. The reduction of inflammatory mediators could cause an increase in the parasitic load in the experimental CCC. However, through the quantification of *T. cruzi* DNA in the spleen, we demonstrated that the treatment with BA5 did not alter the parasitic load **Conclusion**. Our results demonstrate that BA5, through antiparasitic and immunomodulatory action, are potential candidates for the development of new drugs for the treatment of chagasic cardiomyopathy.

Support: FAPESB, CNPq and PRONEX.

Keywords: *Trypanosoma cruzi*, Betulinic acid derivative, Chagas disease cardiomyopathy.

A HISTONE DEMETHYLASE INHIBITOR WITH ANTI-INFLAMMATORY PROPERTIES PRESENTING ANTILHEISHMANIAL ACTIVITY IN A MURINE MODEL OF CUTANEOUS LEISHMANIASIS

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Introduction: Cutaneous leishmaniasis (CL) caused by *L. braziliensis* is the most common clinical form of the disease in Brazil. CL is associated with an intense chronic inflammatory response. The few therapeutic options, the high toxicity and the drug resistance reinforce the need for alternative treatments. Epigenetic mechanisms involving histone modification are deregulated in chronic inflammatory diseases. Thus, epigenetic regulators are considered promising targets for treating these diseases. The present work aims to evaluate *in vitro* and *in vivo* the chemotherapeutic potential of GSK-J4, a histone demethylase inhibitor with anti-inflammatory properties, against *L. braziliensis* in the murine model of cutaneous leishmaniasis. **Methods:** The IC_{50} of GSK-J4 and its reversible inhibition for promastigote forms was determined by flow cytometry and for amastigote forms by direct counting using murine macrophages. A preliminary *in vivo* assay was performed using the BALB/C ear infection model with intralesional GSK-J4 administrations. **Results:** GSK-J4 did not demonstrate cellular toxicity to uninfected host cells up to 100 μM after 24 hrs of treatment. In contrast, the compound showed leishmanicidal effect with IC_{50} of 888 nM for promastigotes and 4.5 μM for amastigotes after 24 hrs of treatment. In addition, treatment with 7.5 μM for 24 hrs showed an irreversible effect on the amastigote form. The intralesional treatment of the compound with 4.5 μM was not able to reduce lesion size and parasitic load on ears and lymph nodes. However, it shows an effect on the development of ulcers, since 75% treated mice did not develop ulcerated lesions. **Conclusions**: So far, data presented here reveals leishmanicidal properties in both evolutionary forms of the parasite without toxicity to the host cell. The next step is to evaluate higher concentrations of GSK-J4 *in vivo* and characterize its anti-inflammatory profile, what could result in higher cure rate and a faster healing time.

Support -IGM

Key words: histone demethylase inhibitor, inflammation, *L. Braziliensis*

ANTI-INFLAMMATORY AND PRO-APOPTOTIC EFFECTS OF PHYTOESTROGEN BIOCHANIN A ON ZYMOSAN-INDUCED ARTHRITIS

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Introduction: Arthritis is an inflammatory disease that causes erosion and remodeling of the cartilage and bone of the joints. It is mediated primarily by neutrophils, which survive in the joint and stimulate a mechanism of death known as NETosis characterized by the formation of extracellular neutrophil traps (TNEs) exacerbating inflammation. The phytoestrogen Biocanin A (BCA) is known for its anti-inflammatory and pro-apoptotic activity, representing a compound with therapeutic potential in the treatment of arthritis. Thus, the aim of the study was evaluated the anti-inflammatory and pro-apoptotic effect of BCA on zymosan-induced arthritis and on neutrophils. **Methods and Results:** Female Swiss mice underwent ovariectomy surgery. The animals were BCA-treated (1, 3 or 9 mg/kg, i.p), or vehicle (saline with Tween) or 17β-estradiol (E2; 50 μg/kg, s.c), for 14 days. Some animals were zymosan-administered with a single intra-articular injection (i.a; 100μg/articular cavity, 30 minutes after the last dose of the treatments). The negative control group received saline (0.9%, i.a.) and another group received dexamethasone (5 mg/kg, s.c) 1 hour prior to zymosan-injection. Paw edema was induced with zymosan-injection (100μg/10 μl, subplantar) 30 minutes after the last dose of BCA (1mg/kg) or E2 (50 μg/kg) for 14 days. Measurements were performed at 0, 1.5, 3, 6, 12 and 24 hours after zymosan-injection. To *in vitro* experiments, neutrophils were isolated from bone marrow, were cultured in medium with or without BCA (1, 10 or 100 μM for 6 hours), for apoptosis evaluation and the NETs formation. All experimental procedures were approved by UFS Animal Research Ethics Committee under number 21/2017. We observed that estrogenic action of BCA altered the animals estrous cycle without changes in uterus weight. BCA (1, 3 and 9 mg/kg doses) reduced the neutrophils infiltrate into the joint cavity in OVX and no OVX animals. BCA (1 mg/kg, i.p) prevented the paw edema formation, reduced cytokine concentrations, TNF-α, IFN-γ and IL-2 and elevated IL-4 and IL-10. The assays *in vitro* demonstrated that BCA (1, 10 and 100 μM) increased neutrophil apoptosis and reduced the NETs extracellular, in dependent-concentration manner. **Conclusion:** BCA exerts anti-inflammatory effect on zymosan-induced arthritis and pro-apoptotic on neutrophil and provide insights for future research on the therapeutic potentials of this phytoestrogen, on the arthritis prevention and progression.

Support: CNPq.

Keywords: Arthritis; Biochanin A; Estrogen; Neutrophils; Apoptosis; NETs

ANTINEOPLASTIC POTENTIAL OF NEW RUTHENIUM-PHOSPHINE COMPLEXES IN HUMAN HEPATOCELLULAR CARCINOMA CELLS HepG2

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Introduction: The ruthenium complexes have anticancer properties, which are selective and present low systemic toxicity. The objective of this study was to analyze ruthenium complexes as drugs for the treatment of cancer. **Methods and Results:** Three new ruthenium-phosphine complexes containing nitrogenous ligands (CBD, CBM and CBT) were tested against cancer cells of different histological types (HepG2, HCT116, SCC4, HSC3, MCF7, K562, HL-60 and B16-F10) and non-cancer cells (MRC5 and PBMC), by blue alamar assay after 72 h of incubation in monolayer (2D) cultures and in a 3D model of multicellular cells formed in HepG2 human hepatocellular carcinoma cells. Subsequently, HepG2 cells were incubated for 24 and 48 h with different compounds CBM and CBT and the number of live cells was subjected to tripan blue analysis. Cell cycle analysis, annexin V staing, quantification of mitochondrial transmembrane potential, and quantification of reactive oxygen species (ROS) were determined by flow cytometry. DNA intercalation assay was performed by fluorimeter. In *in vivo* study, CBM and CBT was injected into C.B.17 SCID mice inoculated with HepG2 cells. The animals were treated at doses of 0.5 and 1 mg/kg for 21 consecutive days. The complexs presented potent cytotoxic effect in cancer cell in 2D and 3D cultures models, where the complexs CBM and CBT were the most potent and selective. HepG2 cells treated with CBM and CBT reduced the number of viable cells, increased the DNA fragmentation, caused loss of mitochondrial transmembrane potential and increased phosphatidylserine externalization, suggesting induction of apoptotic cell death. No increase in ROS was observed. Both complexs were able to intercalate with DNA. In *in vivo* model, inhibition rates of tumor development were 45.4-67.7%. **Conclusion:** In conclusion, the ruthenium complexes tested are cytotoxic to different types of cancer cells, cause DNA intercalation, induce apoptotic cell death in HepG2 cells and are able to inhibit their development *in vivo* in xenograft model.

Support: FAPESB, CNPq.

Keywords: Ruthenium complex, Hepatocellular carcinoma, Citotoxicity, Apoptosis.

EFFECT OF THE PHYTOESTROGEN BIOCHANIN A ON INFLAMMATORY PROCESS DEVELOPED IN OBESE OVARIECTOMIZED MICE.

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Introduction: Adipose tissue is regulated by cytokines and leukocytes profile that define its metabolic state. Adipose tissue hypertrophy promotes hypoxia, alteration of the profile of macrophages to M1, that accumulate around these necrotic adipocytes, characterizing crown-like structures (CLS) (LUMENG, C.N. Mol Aspects Med, v.34, p.12, 2013). The objective was to investigate the effect of the phytoestrogen Biochanin A, little explored in obesity, but, present anti-inflammatory effect, and estrogen on inflammatory parameters in adipose tissue of ovariectomized obese mice. **Methods:** The C57B/l6 were ovariectomy surgery and after 15 days received the following treatments, with a standard diet (OVX+DP), with a hyperlipidic diet (OVX+DH), with a hyperlipidic diet (OVX+DH+E2) and 17-β-estradiol (E2; 50µg/kg; sc; daily) or with Biochanin A (OVX+DH+BCA; 2mg/kg; ip; daily) in the last 4 weeks. The experiment lasted 13 weeks and after that, blood was collected for total and differential leukocyte count and biochemical parameters analysis. The peroxidase activity of eosinophils (EPO) and myeloperoxidase (MPO) were investigated to evaluate the eosinophils and neutrophils migration. Histology of adipose tissue was performed to analyze hypertrophy, hyperplasia and counting CLS. **Results:** E2 replacement reduced glycemia and increased HDL-c and BCA increased only HDL-c, compared to OVX+DH. In leukocyte profile, E2 increased blood eosinophils and EPO in adipose tissue, increased monocytes and reduced total leukocytes and lymphocytes in blood. BCA reduced only neutrophils in blood. Adipogenesis analyzes showed that E2 reduced adiposity index, hypertrophy and CLS. BCA did not prevent hypertrophy, but reduced to CLS and promoted hyperplasia. **Conclusion:** estrogen has anti-inflammatory action in adipose tissue modulating the eosinophils recruitment, and BCA seems to exert this effect on neutrophils.

SUPPORT: CNPq

KEY WORDS: BIOCHANIN A; OBESITY and INFLAMMATION

LINHA 04:

HUMAN NEUTROPHILS PROMOTE REDUCTION IN PARASITE BURDEN IN LEISHMANIA AMAZONENSIS-INFECTED DENDRITIC CELLS VIA DC-SIGN

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Introduction: Leishmaniasis remains as one of the most seriously neglected tropical diseases. This pathology is caused by Leishmania spp. an intracellular parasite. transmitted to mammals through the bite of infected sandflies. During the early events of Leishmania infection. such parasite interacts with a wide range of phagocytic cells such as macrophages. neutrophils. and dendritic cells. Neutrophils play a role in eliciting innate immune responses by releasing inflammatory mediators. or through cell interaction. which collectively recruit and activate other leukocytes. We propose that the DCs might resist to *Leishmania amazonensis* infection due to the activation of appropriated molecular pathways elicited by neutrophil through inflammatory mediators and cell interaction. **Methods and Results:** To test this hypothesis. initially. human monocyte-derived DCs and neutrophils were purified from peripheral blood of healthy donors. Neutrophils were activated with fibronectin at 10 µg/mL for 1 hour while DCs were infected with *L. amazonensis* stationary promastigotes. Subsequently. these cells were co-cultured with (activated or resting) neutrophils in the presence or absence of pharmacological inhibitors of myeloperoxidase (MPO). elastase (NE). metalloproteinase-9 (MMP-9) and α TNFα for 18h. Next. supernatants and cells were harvested to evaluate the release of granules enzymes (MPO and NE) and cytokine production. To evaluate the role of DC activation through cell interaction. DCs were infected in transwell plates at the lower chamber and activated neutrophils were co-cultured in the upper chamber. In other experiments. the co-culture of infected DCs and neutrophils were incubated with anti-DC-SIGN to assess the rate of infection of DCs and parasite burden. Our results demonstrated that the presence of neutrophils is sufficient to promote reductions in the rate of infected DCs and parasite load. however. these alterations were not mediated by the state of activation of neutrophils. Under the inhibition of NE. MMP9. and MPO. there was no reduction in parasite load. despite the increase of MPO and NE in the supernatant of the cells co-culture. **Conclusion:** Collectively. our results suggest that neutrophils reduce DC infection. parasite load. and increase TNF production dependent on cell interaction. through DC-sign. Further experiments will be made to evaluate how neutrophils influence the antigen presentation ability of DCs under infection by *L. amazonensis*.

Keywords: *Leishmania amazonensis*; Dendritic cells; Neutrophil

Foments: Fundação de Amparo à Pesquisa do Estado da Bahia (Fapesb) and CNPq.

SOROPREVALENCE FOR ZIKA. DENGUE AND CHIKUNGUNYA IN PARTURIENTS WHO PRESENTED EXANTEMATIC DISEASE DURING THE GESTATION AND INCIDENCE OF CONGENITAL INFECTIONS IN A MATERNITY OF SALVADOR-BAHIA.

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ABSTRACT: Introduction. Concomitant epidemics of Dengue. Chikungunya and Zika have been occurring in Brazil. In May 2015 the first cases of Zika virus infection (ZIKV) were confirmed in Brazil and after six months an outbreak of newborns with microcephaly was reported in the Northeast. confirming the association with ZIKV infection in pregnant women and congenital infection . Seroprevalence studies. especially in women and pregnant women. are necessary for a better understanding of the impact of these arboviruses in our environment. Methods and Results. We evaluated the prevalence of antibodies to Zika (ZIKV). Dengue (DENV) and Chikungunya (CHIKV) virus in parturients who reported exanthema during pregnancy and in their neonates. This is a cross-sectional. seroepidemiological study. which included parturient women who reported exanthematic disease during pregnancy and their newborns admitted to a reference maternity hospital in Salvador. Bahia. during the Zika epidemic of 2016. Clinical and epidemiological data were obtained with standardized questionnaires after signing the TCLE. Detection of IgG antibodies to ZIKV. DENV. CHIKV and IgM for DENV and CHIKV were performed by commercial ELISA kits (Euroimmun ™). The detection of specific IgM anti-ZIKV IgM was performed by in-house MAC-ELISA (CDC). A total of 101 mothers were included. with a median age of 23 years (IQR = 10). The majority declared to be black (54.5%). and attended high school (46.5%). Regarding seroprevalence. for anti-ZIKV IgM. 07 mothers (6.9%) and 04 neonates (4%) were reagent. For anti-CHIKV IgM. 23 mothers (22.8%) and 04 neonates (4%) were reagent. For anti-DENV IgM. 12 mothers (11.9%) were reagent. The number of seropositive women with IgG against ZIKV. CHIKV and DENV was 73 (72.3%). 39 (38.6%) and 93 (92.1%). respectively. Of the 102 neonates. 06 (8.2%) were born with microcephaly. Among the neonates of the 23 mothers with anti-CHIKV IgM (IgM). 03 had anti-CHIKV IgM. characterizing congenital infection. however they were born healthy. Conclusion. We characterized the seroprevalence rates for ZIKV. CHIKV and DENV in parturients who presented exanthematic disease during pregnancy and the incidence of congenital infection by ZIKV and CHIKV during the study period. Knowledge of seroprevalence for arboviruses is important to understand the real dimension of the arbovirus epidemic in Brazil and to identify groups still susceptible to infections. so that prevention measures can be implemented.

Keywords: Congenital Infection. Seroprevalence. Microcephaly. Zika. Chikungunya

Support: Fundação de Amparo à Pesquisa do Estado da Bahia – FAPESB.

EXPRESSION OF CD86 BY MONOCYTES AND THEIR SUBSETS INFLUENCES THE REGULATION OF THE IMMUNE RESPONSE IN ASYMPTOMATIC PATIENTS WITH CHRONIC CHAGAS DISEASE

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Introduction: In the chronic phase of Chagas disease. 60% of the patients develop the asymptomatic form known as indeterminate (IND). The remaining 30% of the patients develop a life-threatening form in which digestive and/or cardiac alterations take place. The mechanisms underlying the development of severe forms of Chagas disease remain poorly understood. It is well known that interactions between immune cells such as monocytes and lymphocytes drive immune responses. Further. the co-stimulatory molecules CD80 and CD86 expressed by monocytes and subsets induce lymphocyte activation. thereby triggering cellular immune response. Thus. we aimed to characterize the functional-phenotypic profile of monocyte subsets and understand the CD80/CD86 costimulatory expression by monocyte subsets in the protective and/or regulatory immunity against *Trypanosoma cruzi* infection. Here we revealed. for the first time. the functional-phenotypic profile of monocytes subsets in Chagas disease. **Methods and Results:** Using flow cytometry. we evaluated the effect of *in vitro* stimulation with *Trypanosoma cruzi* antigens on the expression of the co-stimulatory molecules CD80 and CD86 in different monocyte subsets of patients with IND and cardiac (CARD) clinical forms of Chagas disease. We also assessed the expression of TLR-2. TLR-4. TLR-9. HLA-DR. IL-10 and IL-12 in the monocyte subsets and of CTLA-4 and CD28. ligands of CD80 and CD86. in T lymphocytes. CD86 expression in all monocyte subsets was higher in IND patients when compared to non-infected individuals (NI). After stimulation with *T. cruzi*. these patients also showed a higher frequency of $CD4^{+}CTLA\text{-}4^{+}$ T lymphocytes than NI individuals. We found an association between CD80 and CD28. and between CD86 and CTLA-4 expression. with a high frequency of Treg cells in IND patients. **Conclusion:** Our data suggest that the binding of CD86 to CTLA-4 and the influence of this co-stimulatory molecule in Treg activation could represent a new strategy to control exacerbated inflammation and avoid tissue damage. Thus. CD86 may be involved in immunoregulation by its association with CTLA-4 and is responsible for the activation of Treg cells in asymptomatic patients.

Keywords: Chagas disease. Monocytes. Immunoregulation

Support: CNPq. CAPES and FAPEMIG.

IL-33 DECREASES IL-1β PRODUCTION IN CUTANEOUS LEISHMANIASIS INDEPENDENT OF IL-10

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Introduction: Cutaneous leishmaniasis (CL) due *Leishmania braziliensis* infection is an inflammatory disease where skin ulcer development is associated with mononuclear cells infiltrate and high levels of inflammatory cytokines. IL-33 is a cytokine that induces Th2 and regulatory responses. Our aim here was to investigate the ability of recombinant IL-33 in modulating the inflammatory response in CL patients. **Methods and Results:** Serum. lesion biopsies and peripheral blood mononuclear cells (PBMC) were obtained from healthy subjects and CL patients. Staining for CD14. CD16. NLRP3 and IL-1β was performed in PBMC. Biopsies and PBMCs were stimulated with either soluble *Leishmania* antigen (SLA) or recombinant IL-33 (rIL-33) for 72 hours. IL-33. IFN-γ. IL-5. IL-13. TNF. IL-1β and IL-6 concentrations were determined by ELISA. It was observed that intermediate monocytes express more NLRP3 and IL-1β intracellularly and that there is exaggerated production of IL-1β by PBMC and biopsies of CL patients. Although IL-33 is not produced by CL patients. the exogenous addition of rIL-33 was able to induce Th2 response and to modulate overproduction of IL-1β. independently of IL-10. Importantly. treatment of infected macrophages with recombinant IL-33 did not interfere on the ability of these cells to kill *Leishmania* parasites **Conclusion:** IL-33 is a molecule with potential immunotherapeutic properties in CL since it is capable of regulating the production of IL-1β in biopsies of CL patients without inhibiting parasite killing.

Keywords: Leishmaniasis. Immunomodulation. Interleukin-33

Funding sources: INCT-DT. CAPES. FAPESB and NIH (AI088650-ICIDR)

PADRONIZATION OF A IMUNOASSAY TO DETECTION OF IMMUNOGLOBULIN A (IgA) AGAINST ANTIGENS OF *PORPHYROMONAS GINGIVALIS* IN SALIVA OF INDIVIDUALS WITH AND WITHOUT HANSENIC REACTION

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Introduction: Leprosy reaction is an inflammatory manifestation whose etiology is associated with alterations in the immune system. possibly in the presence of infectious conditions concomitant to leprosy. such as periodontitis. The aim of this study was to evaluate the IgA-mediated response against antigens of *Porphyromonas gingivalis* (Pg). a micro-organism involved in the pathogenesis of periodontitis. in the saliva of individuals with and without hansenic reaction. **Methods and Results:** 110 salivary samples were obtained with leprosy seen at the Dermatology Clinic of the Professor Edgard Santos University Hospital Complex (HUPES Complex). in Salvador. BA. Brasil. The 110 patients were classified according to the pediodontal diagnostic and the hansenic reaction. For standardization of immunogenicity assays with salivary IgA. five samples of individuals with periodontitis (P) and five samples of individuals without periodontitis (WP) were selected. Their salivary sample were gathered in pools P (05 samples) and WP (05 samples). chosen according to the periodontal clinical parameters that indicated greater severity of periodontitis and better periodontal health. respectively. The measurement of the salivary IgA concentration was carried out by indirect ELISA. The antigens of Pg used in the assays were: the crude extract of the strain ATCC 33277. the recombinant protein HmuY and a synthetic peptide of lys-gingipaína (Kgp12 - IEDB epitope ID 763561). The optimal coefficient between the pool P and the pool WP was determined for each antigen through the ELISA checkerboard. The antigens were analyzed in the following concentrations: Pg extract (2 and 5µg / mL); HmuY (2 and 5 µg / mL) and Kgp12 (5 and 10 µg / mL). All three antigens were recognized by specific IgA and distinguished the pools P and WP. The peptide Kgp12 made better distinction between the pools. presenting a coefficient 5.7. i.e.. the optical density (DO) of IgA in the pool P was 5.7 times greater than the DO observed in the pool WP. The concentrations 5 µg/mL for Kgp12; 2 µg/m for Pg and 2 µg/mL for HmuY showed the best coefficient between pools P and WP. and. therefore were selected for *in vitro* subsequent experiments. **Conclusion:** The coefficient obtained by ELISA checkerboard indicated a differentiation of individuals with periodontitis from those without periodontitis based on the salivary IgA-mediated response. allowing future evaluation regarding the development and description of the immune response to antigens of *Porphyromonas gingivalis* in individuals with and without leprosy reaction.

Keywords: leprosy. periodontitis. Lys-gingipain. HmuY.

Support: LABIMUNO (ICS - UFBA). PPGIm (ICS - UFBA).

MODULATION OF MACROPHAGE MICROBICIDE RESPONSE CAN CONTROL THE INFECTION OF DRUG RESISTANT *LEISHMANIA INFANTUM* ISOLATES

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Introduction: Visceral Leishmaniasis is an infectious disease of neglected people and caused by protozoa *Leishmania*. The control of infection and parasite dissemination is essentially executed by phagocytes like macrophages. the main cell of parasite tropism. However. when the disease is stablished the chemotherapy is the main form of control of the leishmaniasis. But in the last years have been shown increasing cases of treatment relapse patients and *Leishmania* parasites resistant to drug. **Methods and Results:** Thereby. we collected mononuclear cell of peripheral blood of healthy donors (*n* = 7) and differentiate into macrophages. After this. we infected the macrophages with different strains of *Leishmania infantum*: two from relapse patients and naturally *in vitro* drug resistant and one isolated from responsive patient and *in vitro* drug sensitive. Moreover. we treated the infected macrophages with different immune modulators: activators of microbicide response. IFNγ + LPS; macrophage co-activation with recombinant sCD40L; blocking of Interleukin-10 action; inhibition of Nitric Oxide (NO) production by Aminoguanidine. Also. we used pentavalent antimonial treatment. The percentage of infected macrophages and the number of parasites inside of the macrophages was determined by counting of 100 cells into coverslips. From this. our results show the inability of macrophages in control the parasite dissemination only to the resistant isolates at 24h when compared to initial infection (02h). In addition. the use of pentavalent antimonial is unable to control this situation. Interestingly. we observed a significative reduction at 24h in the number of infected macrophages when we treated the macrophages with immune activators or make the co-activation. with IFN + LPS or recombinant sCD40L. Besides. the IL-10 blockade makes the macrophages able to control the parasite dissemination at the 24h time. Moreover. when we inhibited the NO production the number of infected macrophages in 24h was similar the 02h. but we observed an increased number of amastigotes parasitizing the cells. **Conclusion:** the phenotype of drug resistance in *L. infantum* isolates is related to different pattern in macrophage infection and the modulation of immune response of infected macrophages can control the parasites dissemination. These results. open new perspectives to alternative control of treatment relapses cases of visceral leishmaniasis.

Keywords: leishmaniasis; drug resistance; immune response.

Support: CNPq. CAPES. FAPITEC. NIH.

THE ROLE OF NEUTROPHILS IN SUBCLINICAL INFECTION DUE TO *Leishmania braziliensis*

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Introduction: Human cutaneous leishmaniasis (CL) due to *Leishmania braziliensis* is characterized by a skin lesion and an inappropriately modulated inflammatory response that is associated with the pathogenesis. Individuals with subclinical infection (SC) present evidence of immune response against the parasite but do not develop disease. Previous studies have shown the participation of innate immune response in the control of the infection. Despite neutrophils are the first cells to migrate to the site of infection. studies have shown these cells may participate in CL pathogenesis. The main objective of this study was to investigate the role of neutrophils in SC infection. **Methods and Results:** Neutrophils activation and production of oxidative burst were evaluated by flow cytometry. parasite infection by optical microscopy and gene expression after RNA sequencing. Lower expression of CD62L and higher expression of TLR2/4 showed that neutrophils from SC individuals were more activated as compared to cells from CL patients. Also. neutrophils from SC were less permissive for infection and produced lower amount of oxidative burst and ROS than neutrophils from CL patients. The analysis of gene expression showed that when the groups were compared. 8 genes were differently expressed and 2 of them were associated to 12 metabolic pathways. *CASP1* and *BTN3A3* were downregulated in neutrophils from SC individuals and were identified in pathways related to CL pathogenesis. Genes associated with increasing in neutrophils survival. cellular migration. protein synthesis and transport and to immediate early response were identified as well. According these results. neutrophils from SC individuals are more activated. able to control the infection and present differences in gene expression as compared to CL cells. **Conclusion:** Thus. neutrophils from SC individuals may influence the response against *L. braziliensis* related to the control of infection and absence of the disease.

Keywords: *Leishmania braziliensis*. Cutaneous Leishmaniasis. Subclinical Infection. Neutrophils. RNA-Seq.

EFFICACY OF PHOTOACTIVATED EXTRACT OF *Myrciaria cauliflora* AGAINST *Staphylococcus aureus* INFECTION

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Background: *Staphylococcus aureus* is one of the major microorganisms that cause human diseases. leading from mild skin infections to serious infections. It has already been shown that photodynamic therapy is capable of inactivating MRSA strains. Therefore. the research or development of new photosensitizers becomes important. Thus. this work brings. in an innovative way. the use of extract of *M. cauliflora* as a photosensitizer. comprising its use as an antimicrobial agent when activated by light. against *S. aureus*. **Methods:** Twenty microliters of solutions of the extract of *M. cauliflora* 2 mg/mL were applied to each of the disks and the plates were incubated at 37°C for 24 hours. Subsequently. in a model of intradermal infection in Balb/c mice. 10^7 CFU of MRSA were inoculated in the left ear of these. The euthanasia of the animals occurred 24 hours after the treatment and the draining lymph nodes were collected as well as the infected ears. **Results:** Thus. it was observed that the crude extract of *M. cauliflora* increased antibacterial action when stimulated by LED light *in vitro* and *in vivo* also by reducing the bacterial load on the lymph node. Other aspects were observed as after being photoactivated the extract of *M. cauliflora* promotes an *in vivo* release of TNF-α and reduction of all other cytokines analyzed. In addition. enhances the expression of E-cadherin and Myeloperoxidase. **Conclusions:** In view of the results analyzed. extract of *M. cauliflora* is an important promising photosensitizer for use in antimicrobial photodynamic therapy against *S. aureus*.

Keywords: *Staphylococcus aureus***;** photodynamic therapy; photosensitizers; *Myrciaria cauliflora*.

SYSTEMS BIOLOGY APPLICATION TO DENTIFY IMMUNOATIVATION MARKERS AND VIRAL EVOLUTION OF CHIKV. DENV AND ZIKAV INFECTIONS

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Introduction: Chikungunya. Dengue and Zika virus are the most circulating arboviruses in Brazil today. The clinical presentations of these three arboviruses are similar. including fever. myalgia. maculopapular rash. pruritus and arthralgia. The no specific symptoms make it difficult to distinguish the pathogen during the acute phase of each disease. However. the clinical course and risks of complications are different among arboviruses throughout the infection. **Methods and Results:** In collaboration with the Secretariats of Health of the cities of Campo Formoso. Senhor do Bonfim and Itabuna. in the state of Bahia. we are carrying out a study involving individuals with suspected acute arboviruses. Acute infections are defined by RT-qPCR for each of the arboviruses. From this. we are performing complete virus genome sequencing by the MinION platform and evaluation of the transcriptional response by the Illumina platform. In addition. we will also quantify plasma soluble cytokines and inflammatory cascade enzymes. **Conclusion:** In this study. we intend to identify viral and immunological markers that are associated with Chikungunya. Dengue and Zika virus. and then contribute to the elucidation of immune activation and interaction with the viral diversity of arbovirus infections.

Keywords: arboviruses. NextSeq. RNAseq

Support: CAPES

EVALUATION OF IMMUNORREACTIVITY OF DOMICILIARY CONTACTS OF TUBERCULOSIS PATIENTS BY THE INTERFERON-GAMA RELEASE TEST (IGRA).

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Introduction: Quantiferon® (QFT. Cellestis) is a test used to diagnose infection caused by Mycobacterium tuberculosis. Its performance is superior to that of the currently used tuberculin test. since its outcome is not influenced by previous vaccination with M. bovis Bacillus from Calmette-Guérin (BCG). We evaluated the QFT performance in the detection of tuberculosis infection in patients newly diagnosed with positive smear-positive pulmonary tuberculosis (TB). as well as in the detection of infection among their household contacts. **Methodology and Results**: Patients over 18 years of age diagnosed with pulmonary TB (indexes) and their respective contacts between 7 and 24 years of age were enrolled in health units with TB control program in Salvador-Bahia. The contacts should have lived with the index case for at least seven consecutive days during the three months prior to the diagnosis of tuberculosis in the index case. Volunteers with negative QFT were followed up longitudinally and reevaluated after two. six and twelve months or until conversion to positive test in the same interval. 97 volunteers were recruited (40 index cases and 57 contacts). A positive QFT was obtained in 38 (95%) of the index cases. while 2 (5%) were negative. Among the contacts. 33 (58%) presented negative QFT and were included in the cohort. To date. 27 of these contacts have already been submitted to the second evaluation (two months after recruitment). After six months. 19 volunteers who were QFT-negative within two months were reassessed. of which 15 (79%) remained negative in this third evaluation. Follow-up was completed for thirteen volunteers (at 12 months post-recruitment): 4 remained negative and 6 were on-going. The conversion of the test was observed for six volunteers between time zero and two months (17%). as well as for a volunteer between 2 and 6 months (5%). These results suggest index case infection or late detection of individuals who were already infected at time zero due to insufficient QFT sensitivity. **Conclusion**: Our results are consistent with a good sensitivity of QFT to identify TB infection in a sample of patients in whom comorbidities are not frequent. as well as immunosuppressive conditions are not expected.

Keywords: Latent tuberculosis; Interferon-gamma release assay (IGRA); household; Performance.

Support: FAPESB. PIBIC-FIOCRUZ.

IDENTIFICATION OF NEW INHIBITORS OF ARGINASE FOR THE *LEISHMANIA AMAZONENSIS* INFECTION

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Introduction: Cutaneous Leishmaniasis. caused by Leishmania. affects millions of individuals worldwide. Despite its side-effect and cytotoxicity. antimonial remain the first choice treatment. In order to discover novel leishmanicial substance *in silico* approaches (pharmacophore models) were employed to identify putative inhibitors of arginase. a key enzyme in polyamines biosynthesis that is essential for parasite proliferation. Among the drugs identified. we selected the potential arginase inhibitors with the best coupling score and solubility to proceed with the *in vitro* studies. Here. we report assays performed to evaluate the biological effect of S783579. M5171 and A4021 in the context of *Leishmania amazonensis* infection of human macrophages derived from monocytes. **Methods and results:** First. the axenic culture of promastigotes in the stationary phase of *L. amazonensis* was incubated with S783579. M5171 and A4021 at different concentrations (0.001. 0.01.0.1. 1. 10.100. 500 μM / ml and 1M / ml) and proliferation was monitored for 120h through direct counting in optic microscopy. We detected a reduction in parasites proliferation at the highest concentrations used. Next. we evaluated the axenic culture toxicity of *L. amazonensis*. For this. we evaluated cell death patterns in promastigotes treated with 100 μM of the compounds by fluorescence microscopy. After 72 h of treatment. we incubated with acridine orange (100 μg / ml) and propidium iodide (100 μg / ml). It was observed a nuclear dilatation and propidium iodide staining by the change in membrane permeability suggesting that the drugs cause secondary necrosis or late apoptosis. In addition. we evaluated the effect of M5171. S783579 and A4021 on parasite-host interaction. Therefore. we infected human macrophages derived from monocytes with *L. amazonensis* and treated with drugs (100 μM) for 72 hours and estimated the viability of promastigotes by optic microscopy. Although the compounds showed leishmania toxicity. in assessing the viability of human macrophages by MTT. they did not show cytotoxicity after 24 hours of treatment at any of the concentrations tested. **Conclusion:** Through the results found concludes that S783579. M5171 and A4021 are able to reduce the proliferation of *L. amazonensis* and interfere in the viability of the parasite. In addition. the low toxicity in human macrophages derived from monocytes make them good candidates for the development of new treatments for cutaneous leishmaniasis.

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ANALYSIS OF MOLECULAR EPIDEMIOLOGY AND PATHOGENESIS OF CLINICAL ISOLATES OF *Ureaplasma diversum*

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Introduction: *Ureaplasma diversum* is a pathogen found genital tract of cattle**.** Is associated with genital disorders such as infertility. placentitis. abortion. birth of weak calves. low sperm motility. seminal vesiculitis and epididymitis. Studies evaluating the genetic diversity of strains of *U. diversum* and their influence on the immune response are poorly explored in cattle. Therefore. to better understand the genetic relationships of different strains with the pathogenicity of *U. diversum*. the Multilocus Sequence Typing (MLST) scheme was used to characterize ATCC 49782 and another forty four isolates obtained from different Brazilian states. **Methods and Results**: The forty-five Strains were cultured and the DNA extracted. Primers were designed for housekeeping genes *ftsH. polC. rpL22. rpoB. valS* and *ureA* and for virulence genes. phospholipase D (*pld*). triacylglycerol lipase (*tgl*). hemolysin (*hlyA*). MIB-MIP system (*mib-mip*). *mba*. *VsA* and ribose transporter (*tABC*). PCRs were performed and the housekeeping gene products were purified and sequenced. STs. CCs were assigned and the phylogenetic relationship was also evaluated. Thus. a total of 19 STs and 4 CCs were observed. Following the molecular analysis. six distinct strains of *U. diversum* were selected. inoculated into bovine monocyte / macrophages culture and evaluated for gene expression of the cytokines TNF-α. IL-1. IL-6. IL-10 and IL-17. Differences were observed in the induction of cytokines. especially between strains 198 and BA78. which induced inflammatory and anti-inflammatory profiles. respectively. and also differed in virulence factors. BA78 did not exhibit only one gene. whereas no factor was detected in strain 198. **Conclusion:** In conclusion. we observed intra-species variability among strains of *U. diversum* induced different immunological responses.

Keywords: *Mollicutes.* diversidade. tipo de sequência. complexo clonal. expressão gênica. citocinas.

Support: CAPES

EFFECTS OF AEROBIC EXERCISE TRAINING ON CHRONIC CHAGASIC CARDIOMYOPATHY IN AN EXPERIMENTAL MODEL

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Introduction: Chronic Chagasic Cardiomyopathy (CCC) is a disease caused by parasite *Trypanosoma cruzi*. The cardiac remodeling associated to CCC induces arrhythmias. hypertrophy and / or dilation of the left ventricle and tissue fibrosis. which leads to contractile capacity impairment. There is no specific treatment for CCC. which makes its course life threatening culminating in heart failure. It has been described that aerobic exercise training (AET) was beneficial in heart failure patients. however. in individuals with CCC the effects of AET were not fully elucidated. In the present work. were investigated the effects of AET on CCC through functional and structural cardiac analysis and the molecular mechanisms involved in these processes. **Methods and Results:** C57BL / 6 chagasic mice were submitted to 5 weeks of AET. 5 times a week. with progressive intensity. Cardiac function analysis was performed by echocardiogram and electrocardiogram. before and after the AET. The gene expression of mRNAs and miRNAs was performed by RT-qPCR in samples of cardiac tissue. Morphometric analysis and detection of inflammation and fibrosis markers were performed by immunofluorescence of cardiac and skeletal muscle tissue samples. **Results and Discussion:** Regard to EKG analyses all chagasic mice developed arrhythmias with different degrees of severity. AET improved arrhythmias in 43.75% of trained mice. only 12.5% got worse and the remaining did not change. Non trained chagasic mice had non improvement in arrhythmias.Non infected mice had no arrhythmias. AET induced reduction of the gene expression of TGF-β. TNF-α. IL-1β. MMP-9. IL-6 and PTPRC. AET did not modulates the expression of miR-21. miR-29. miR-146a and miR-155. AET reduced cardiac and skeletal muscle fibrosis. but did not decrease the inflammation of these tissues. Thus. AET induces an antiremodeling effect by decreasing tissue fibrosis. **Conclusions:** This study suggest a new intervention in chagasic patients. aimed attenuating the progression of the disease and reducing fibrosis through AET.

Keywords: Chagas Disease; Chronic Chagasic Cardiomyopathy; Aerobic Exercise Training.

Support: FAPESB. CNPq.

EXPRESSION OF IL-10 BY T CD4$^+$ REGULATORY LYMPHOCYTES IN PATIENTS WITH ADVANCED FIBROSIS PERIPORTAL + PULMONARY HYPERTENSION SECUNDARY TO *SCHISTOSMA MANSONI* INFECTIONS

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Introduction: Schistosomiasis is a parasitic disease that affects about 240 million people around the world. It is estimated that 5-10% of individuals develop into severe forms of the disease. The chronic phase of the disease is associated with Th2 type response. but evidence also suggests the participation of Th1 and Th17 cytokines in the severity of the disease. Our objective was to evaluate the CD4 T lymphocyte profile of patients with the severe forms of schistosomiasis. **Methods:** Peripheral blood mononuclear cells were stimulated with soluble egg *Schistosoma mansoni* antigen (SEA). Expression of surface molecules and cytokines in the lymphocytes were performed by labeling with monoclonal specific antibodies and acquired by flow cytometry. Twelve subjects were recruited for the evaluation of immunology. and 5 subjects were classified without fibrosis and 7 with incipient fibrosis not excluded (WF/IFNE). 10 with periportal fibrosis and 3 with possible periportal fibrosis (PF/PPF). 2 with advanced periportal fibrosis and 2 with advanced periportal fibrosis with portal hypertension (APF/APF+PH). Lymphocytes were obtained by separation of PBMCs and analyzes of the molecules and cytokines were performed by flow cytometry. **Results:** It was observed that the PF/PPF individuals had higher mean fluorescence intensity (MFI) of the IL-4 and IL-5 cytokines compared to the WF/IFNE individuals. as well as. these individuals presented higher MIF of the cytokines IFNγ and IL-17 compared to the SF / FINE group ($p < 0.05$). In addition. the PF/PPF group showed higher MFI of GITR and CTLA-4 molecules compared to the WF/IFNE group ($p < 0.05$). We also observed that MFI of IL-10 expressed by CD4$^+$CD25^{hi} lymphocytes among individuals with APF/APF+PH was higher than individuals with PF/PPF ($p < 0.05$). In addition. the PF/PPF group had a higher frequency of CD4$^+$CD25^{hi} cells compared to WF/IFNE individuals. **Conclusions:** Individuals with periportal fibrosis showed an increase in Th1. Th2 and Th17 cytokines by CD4$^+$ T lymphocytes. while the group of patients with advanced periportal fibrosis + pulmonary hypertension presented a regulatory profile associated with production of IL-10 by regulatory T cells.

Keywords: Liver Fibrosis**.** Shistosomiasis. CD4$^+$ T Lymphocytes

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Toxocara sp. AND *Ascaris lumbricoides* INFECTION INFLUENCE CLINICAL MARKERS IN INDIVIDUALS BEARING SEVERE ASTHMA

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Introduction: Helminth infections are responsible for inducing a strong Th2 response mostly by IgE and eosinophilia production and they may cause respiratory tract inflammation in asthmatics. In this context. *Toxocara sp*. and *Ascaris lumbricoides* have been associated with the imune response regulation in individuals bearing severe asthma increasing the eosinophil and IgE levels by producing IgG and IgG4 antibodies. The way how *A. lumbricoides* IgG4 antibodies can contribute to imune response regulation is more studied when it is compared to *Toxocara sp*. IgG antibodies. In this study were have analysed associations between IgG antibodies anti-*Toxocara* spp.and anti-*A. lumbricoides* IgG4 antibodies and their influence in clinical markers of individuals bearing severe asthma. **Methods and Results:** 176 sera from PROAR (program for asthma control from UFBA) patients with severe asthmatic patients according to GINA questionnaire were analyzed by ELISA to detect IgG and IgG4 production by *Toxocara sp.* and *A. lumbricoides* infection (respectively). Information about blood eosinophils. allergen specific IgE (sIgE) levels and atopy were obtained from PROAR database. The statistical analyses were performed by SPSS 20.1. There was no association between individuals with *Toxocara* sp. positivity (89 individuals; 58%) and eosinophils higher than 260. 300 and 450/ml and were associated with low risk estimation (OR= 1.51; 95%; CI 0.82-2.75; OR= 1.57; 95%; CI 0.86-2.86; OR= 1.65; 95%; CI 0.91-2.99. respectively). however. the there was a positive and statistically significant correlation between *Toxocara* spp seropositivity and the number of blood eosinophils ($p = 0.027$). while the correlation between *Toxocara* seropositivity and sIgE levels was not significant ($p = 0.411$). There was an association between anti-*A. lumbricoides* IgG4 seropositivity (17 individuals; 9.7%) and blood eosinophils higher than 260. 300 and 450/ml (OR= 3.96; 95%; CI 1.09-14.3; OR= 4.49; 95%; CI 1.24-16.24; OR= 5.09; 95%; CI 1.41-18.4. respectively). The correlation between *A. lumbricoides* positivity and the number of eosinophils/ml and IgE levels was also significant ($p = 0.003$ and $p < 0.01$. respectively). No associations were found between seropositivities to both helminthes and atopy. **Conclusion:** These results found that both parasites seropositivities increase blood eosinophils in asthmatic patients. but *A. lumbricoides* seropositivity had a more strong action. Possibly because the antibody used as marker of the infection was IgG4. which occurs during the active infection while the IgG used as marker of *Toxocara* infection stands for both active of post-infection phases.

Support: *CN*Pq.

Keywords: ELISA. eosinophils. helminth

REVERSE VACCINOLOGY IN MURINE MODEL AND CANINES FOR THE CONTROL OF *Toxocara canis* INFECTION

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Introduction: Toxocariasis is a zoonosis of global importance recently considered by the US Centers for Disease Control and Prevention (CDC) as one of the five most neglected parasitic infections of the human being. Infection with *Toxocara* spp. in pets and the spread of their eggs in feces are of great importance for public health. To date. there is no program to control this infection and vaccination can be a good tool to achieve this goal. **Methods and Results:** From the genome and proteome of *Toxocara canis*. in an in silico analysis. 8 proteins of immunogenic interest were selected. These proteins were expressed in purified bacterial vectors and are being tested in a murine model. in a project already underway. The best proteins will be used to immunize C57-Black mice using different adjuvants (Gardiquimod VacciGrade™. Aluminum Hydroxide®. Quil-A® and AS01®); for this. 4 groups of 7 mice will be immunized with three doses of the emulsified proteins in each of the adjuvants with a 15 day interval; 1 group will be inoculated with the proteins without adjuvant and 1 group will be exposed only to PBS. Then all groups will be inoculated orally with 500 larvae of *T. canis*; measurement in serum of IgM. IgA. IgE using indirect ELISA and capture ELISA for cytokine IFN-γ. TNF. IL-14. IL-5. IL-13. IL-13. IL- 10 and TGF-β in splenocyte culture supernatants; analysis of the number of larvae in tissues will also be performed. The best group will be selected for investigate the potential of the antigens tested in immunoprophylaxis and immunotherapy canine toxocariasis. To this. 18 beagle dogs will be used; one group will receive the three doses of the experimental vaccine with a 15-day interval; other 2 groups will only receive PBS in the same scheme of applications of group 1; all dogs 21 days later will be inoculated orally with 500 larvae of *T. canis*; 21 days after one of the PBS groups will receive the same vaccine regimen as group 1. Serums from dogs to be collected on days 0. 7. 14. 21. 42. 84. 168. 336 postinfection will be assayed by indirect ELISA to determine the concentration of anti-T IgG antibodies. RNA from peripheral blood mononuclear cells cultured in vitro will be obtained for expression of the INF-γ. TNF. IL-4. IL-2 and IL-12 cytokines by RT-PCR; the parasite load will be determined by coproparasitology. **Conclusion:** It is hoped that this project will have as a product a vaccine/immunotherapeutic for toxocariasis that can be used for dogs. thus reducing the environmental contamination with eggs of this parasite which may have an impact on the control of human toxocariasis.

Support: RENORBIO/CNPq and Laboratório de Alergia e Acarologia-UFBA.

Keywords: toxocariasis. immunoprophylaxis. immunotherapy. vaccine. zoonoses.

CHARACTERIZATION OF THE ANTIGENIC POTENTIAL OF RECOMBINANT PROTEINS OF *Corynebacterium pseudotuberculosis*

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Introduction: The caseous lymphadenitis (LC) caused by *C. pseudotuberculosis* is a chronic infection disease which mainly affects sheep and goats. Because the initial symptoms are not immediately obvious. the clinical diagnosis is not effective. A number of serological tests have been developed to detect the disease in asymptomatic animals and enzyme-linked immunosorbent assay (ELISA). One of the most used due to its advantages: cost-effectiveness. applicability. acceptable sensitivity and specificity. Various ELISAs using different antigenic preparations have been tested. however. few use recombinant proteins for the diagnosis of LC. which could confer higher levels of specificity associated with significant sensitivity values. since they use a single purified antigen. Recombinant antigens DTx. Trx. TrxR. LexA. NanH. SodC. PknG and SpaC can represent a promising alternative to control the LC. Methods and Results: The recombinant proteins DTx. Trx. TrxR and LexA. were kindly provided by the group of Universidade Estadual Paulista. Institute of Biosciences. São Paulo. The proteins NanH. SodC. PknG and SpaC were produced in LABIMUNO. UFBA. The purity of the recombinant antigen was assessed by 12% SDS-PAGE. Recombinant proteins were tested against sera from 16 goats. The animals were divided into 3 experimental groups: 1- infected biofilm-forming strains; 2- infected with strain not forming biofilm; 3- controls (non-infected). The sera of these animals were assessed 90 days after infection. Indirect ELISA test was applied to detect specific IgG antibodies anti-*C. pseudotuberculosis* in goats. The cut-off point was set by the ROC curve (Receiver Operatos Characteristic). In the ROC curve analysis of recombinant proteins DTx. Trx. TrxR. LexA. NanH. SodC. PknG and SpaC obtained sensitivity values of 70%. 90%. 90%. 70%. 70%. 100%. 100% and 60%; and a specificity of 67%. 50%. 83%. 50%. 67%. 100%. 100% and 33%. respectively. Conclusion: The recombinant proteins SodC and PknG shown promising results in the diagnosis of LC (100% sensitivity and specificity). These proteins will be tested with ~700 sera from naturally infected goats and sheep in order to assess their antigenic potential in a larger sample size.

Support: FAPESB. LABIMUNO-UFBA.

Keywords: *Corynebacterium pseudotuberculosis*. Caseous lymphadenitis. Recombinant proteins.

IMMUNE RESPONSE INDUCED BY RECOMBINANT PROTEINS OF *Corynebacterium pseudotuberculosis* IN EXPERIMENTALLY VACCINATED GOATS

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Introduction: Caseous lymphadenitis (CL) is a chronic disease responsible for significant economic losses in sheep and goat breeding worldwide. The treatment for this disease is not effective. and an intense vaccination schedule would be the best control strategy. **Methods and Results:** In this study. we evaluated the associations of eight recombinant proteins from *Corynebacterium pseudotuberculosis* (rSpaC. rPknG. rNanH. rSodC. rDtx. rLexA. rTrx and rTrxR) as subunit vaccines in goat. Four experimental groups (6 animals each) were immunized with rSpaC + rPknG + rNanH + rSodC adjuvanted with Montanide ISA 61 VG (G1); rDtx + rLexA + rTrx + rTrxR adjuvanted with Montanide ISA 61 VG (G2); rSpaC + rPknG + rNanH + rSodC+ rDtx + rLexA + rTrx + rTrxR adjuvanted with a attenuated strain of *C. pseudotuberculosis* – T1 (G3); and with a sterile 0.9% saline solution (G4). The goats received two doses of each vaccine at a 30-day interval. Blood samples were collected every two weeks and serum samples. from all the animals. were evaluated by indirect ELISA against all the proteins used in the vaccines composition. The total IgG production level sharply increased after the first dose of vaccination in the experimental groups that received the vaccines ajuvanted with Montanide ISA 61 VG. While in the group vaccinated with all the recombinant proteins and adjuvanted with T1 attenuated strain. the increased of IgG level was observed only 30 days after the first dose. All the groups showed a humoral immune response against all antigens of the vaccine formulations. **Conclusion:** Thus. all the different vaccines associations were able to induced humoral immune response in goats. For the next stages of the experiment. these vaccines will be evaluated regarding their capacity of protection after a challenge infection from these animals with a pathogenic strain of *C. pseudotuberculosis.*

Keywords: Caseous lymphadenitis. recombinant proteins. vaccine.

Support: CAPES. FAPESB and LABIMUNO-UFBA.

ANTI-LJM11/LJM17 ANTIBODIES AS BIOMARkers of susceptibility to Canine visceral leishmaniasis IN DOGS followed IN An ENDEMIC AREA

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Introduction: Visceral leishmaniasis is transmitted by *Lutzomyia longipalpis*. Vector saliva plays an essential role in the transmission of *Leishmania*. Our role was to evaluate the reactivity for recombinant proteins rLJM11. and rLJM17 in sera from dogs followed for two years in a cohort study into a CVL endemic area. **Methods and Results:** The animals were reevaluated every 6 months for CVL diagnosis. clinical and vector exposure evaluation. and cytokines quantification. rLJM11+17 ELISA assessed vector exposure. Animals were classified as reexposed when presented anti-saliva antibody levels doubled or more among evaluations. Parasite load quantification was assessed by qPCR and ELISA was performed for cytokine and chemokine quantification. Animals were classified as negative. resistant and susceptible to CVL based on clinical scores and CVL diagnosis during follow-up. A total of 285 animals were included in the study. and 111 completed all surveys. Among them. 46 animals presented negative results for saliva exposure and 19 were also negative for CVL at the beginning of the study. After 6 months. the majority (70%) of the 46 animals that started as unexposed were exposed to the vector. The increase in the incidence of exposure during follow-up was followed by an increase in the incidence of CVL cases. Most of the animals (63%) were reexposed to the vector. There was an association between reexposure to vector and risk of *Leishmania* infection and reexposed dogs had twice more chance to be susceptible. Susceptible dogs had higher levels of anti-saliva antibodies. There was a positive correlation among antibodies levels against saliva and skin parasite load. Reexposed animals had higher levels of TNF-α. IL-2. IL-7. IL-15. IL-18. KC and MCP-1 when compared to their pre-reexposure levels. **Conclusion:** The production of anti-rLJM11 and rLJM17 antibodies proved to be a useful marker of vector saliva exposure; additionally. we observed an association between vector reexposure and greater susceptibility to CVL.

Support: FAPESB and CNPq.

Keywords: cohort. *Leishmania*. recombinant proteins. saliva. vector

LOW MOLECULAR WEIGHT FRACTION OF FUNGUS *Trichoderma asperelloides* AFFECT THE SURVIVE OF *Leishmania amazonensis* AMASTIGOTES IN J774 MACROPHAGES

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Introduction: American Cutaneous Leishmaniasis (ACL) represent a public health problem affecting thousands of people around the world every year. The toxicity and difficulties inherent to administration of treatment against ACL has been reported. as well increased pathogen resistance. Because of that researches for potential molecules with medical application is needed. In this sense the diversity of secondary metabolites produced by species of *Trichoderma* genus with medical applications represent a potential way to development of new pharmacological active molecules. **Methods and Results:** In this work. we evaluated the effect of low molecular weight fraction of ethanolic extract of fungus *Trichoderma asperelloides* ($LMWF_{ExtrTA}$) against *Leishmania amazonensis* forms. To evaluate the effect of $LMWF_{ExtrTA}$ on proliferation of *L. amazonensis* and survive of J774 macrophages we performed cell viability assay with MTT and phagocytosis assay. The results have shown significative reduction on viability of promastigote. indicating a leishmanicidal effect. Next. we assessed if the $LMWF_{ExtrTA}$ affect the morphology of promastigotes and proliferation of amastigotes in macrophages with transmission electron microscopy (TEM) technic to elucidate the ultrastructural changes in protozoa submitted to compound. Morphological alterations were detected in the flagellar pocket of promastigote. also highlighting the action in the control of amastigotes proliferation. **Conclusion:** This is the first report revealing a chemotherapeutic potential of this fungal compound for the treatment of ACL.

Keywords: Chemotherapeutic potential; Biotecnology; Endophthy fungus

Support: CAPES and UESC

ALTERNATIVELY ACTIVED ANTIGEN PRESENTING CELLS MODULATES IMMUNE RESPONSE IN CHAGAS DISEASE IN VITRO

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Introduction: Chronic chagasic cardiomyopathy (CCC) is present in 30% of *Trypanosoma cruzi*-infected people who are in the chronic phase of the infection. The CCC is a pathogenic process characterized by myocardial damage. associated with inflammation and fibrosis caused by the multifocal parasitism and may be occasioned by adverse immune reaction. Several treatments are under development of reducing the progression of CCC. Antigen presenting cells (APCs) are dendritic cells and macrophages and are important mediators for induction of effective responses and maintenance of immune tolerance. according to microenviroment. The aim of the study was to evaluate the action of alternatively activated APCs (aaAPCs) on the modulation of the immune response in Chagas disease in vitro. **Methods and Results:** Alternatively actived APCs were produced from bone marrow of C57Bl/6 mice. in medium supplemented with 30% of GM-CSF and dexamethasone. activated with 1 ug/ml of bacterial lipopolysaccharide for 24 h. The aaAPCs was co-culture with splenocytes of naïve and infected C57Bl/6 for 72h at 37°C with 5% CO^2. in triplicate. Cell proliferation was evaluated 1 µCi of 3H-thymidine was added to each well. and the plate was incubated for 18 h. The levels of cytokines (IL-2 and IL-10) were measured by ELISA. For Treg cell analysis by flow cytometry. the cells were stained with anti-CD4 (Fitc). anti-CD25 (APC) and then FoxP3 (PE). Lymphoproliferation analysis showed decrease in proliferation of infected splenocyte when in contact with aaAPCs. In addition. cultures with alternatively actived APCs produced less IL-2 and more IL-10. and we shown increased the Foxp3+ Treg cell population in aaAPCs and splenocyte chagasic (1:10). **Conclusion:** These results imply that the aaAPCs have a potential in modulating the immune response in Chagas disease.

Keywords: *Trypanosoma cruzi*. Cardiomyopathy. alternatively activated APCs.

Support: Fiocruz. CAPES and CNPq

EXPRESSION OF mIR-223. mIR-133a AND mIR-7 IN PATIENTS WITH AMERICAN CUTANEOUS LEISHMANIASIS

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Introduction: Leishmaniasis are tropical parasitic diseases caused by different species of the genus *Leishmania*. considered public health problems. because they are complex clinical and epidemiological diseases. American Cutaneous Leishmaniasis (ACL) is particularly important in South America by presenting aspects of chronicity and to develop metastases that lead to difficult clinical conditions. It is known that after infection are altered factors that influence the immune response of the host. deregulating the expression of inflammatory mediators and also of genes that encode microRNAs (miRNAs). which are small endogenous nucleotides and important regulators of the cellular and molecular mechanisms. During the course of the disease. changing the expression of these genes can lead to a susceptibility in the development of the lesion. The present study had as objective the evaluation of the expression of microRNAs in patients with Cutaneous Leishmaniasis . **Methods**: We used plasma samples from patients with active lesions. considered positive by the Montenegro intradermal reaction and control patients. All samples were subjected to RNA extraction. quantified. and subsequently obtained the cDNA by reverse transcriptase. The quantification of the levels of expression of miRNAs evaluated was obtained by qPCR in Real Time. **Results**: There was a significant difference in the variation of the levels of miR-223. miR-133a and miR-7 in relation to the studied groups. being a high expression in positive patients. The literature and silico prediction relate this microRNAs likely involved in mechanisms of inflammasomes activation. **Conclusion**: These results suggest that expressed microRNAs may play an important role in regulating the host immune response during leishmania infection. serving as biomarkers in leishmaniasis and contributing to the understanding of mechanisms of gene regulation in the host during the disease.

Keywords: Cutaneous leishmaniasis. microRNAs. Inflammasome

Support: FAPESB. UESC

LINHA 05:

POLIMORPHISMS IN *GATA-3* AND *STAT-6* ARE ASSOCIATED WITH ALLERGIC DISEASES IN A BRAZILIAN POPULATION

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Introduction: Asthma is considered one of the leading and most common chronic respiratory disease. The characteristic lung inflammation of asthma is the interaction between allergens with type 2 profile cells that stimulate the immune system to produce interleukins that aid in the inflammatory process. As an example of these cytokines we have IL-4, IL-5 and IL-13 that contribute to the manifestation of asthma symptoms whose production is stimulated by the transcription factors STAT-6 and GATA-3. Considering that it is a disease with genetic influence whose causal factors are not yet fully elucidated, studies of genetic polymorphisms can provide important information on the heterogeneity of asthma. **Objectives:** The aim of this study was to associate polymorphisms (SNPs) in GATA-3 e STAT-6 genes with asthma and allergy markers in an admixed population of northeastern Brazil. **Methodology:** The study was conducted with 1246 participants in the Social Changes Program, Asthma and Allergy in Latin America (SCAALA). The genetic material was extracted from volunteers' whole blood samples and genotyping was performed through the Illumina Human Omni 2.5-8 BeadChip Kit. The chi-square test was performed between allele frequency in cases and controls to obtain unadjusted nominal p-values. Empirical p values were generated by permutation using PLINK software. For adjusted association tests, logistic regression was corrected for appropriate covariates (such as sex, age, and helminth infection). **Results:** In the STAT-6 gene, 5 SNPs were found and 4 SNPs presented p <0.05. In the GATA-3 gene, of the 49 SNPs present in the analysis, 39 presented p <0.05. For the STAT-6 gene of 4 significant phenotypes 2 were associated with two or more allergy and / or asthma markers (rs79982039 and rs4759031). The GATA3 gene, among the 39 significant, 15 had association in two or more markers of allergy and / or asthma (rs263425, rs521143, rs2240254, rs2228254, rs11567920, rs115515044, rs10508340, rs1244181, rs3781092, rs1399180, rs71481756, rs3781093, rs74123884, rs35597056, rs4143094). Conclusion: Our results demonstrate that variants of the STAT-6 and GATA-3 genes may affect the occurrence of asthma and allergies in our population. Therefore, further functional analysis may be performed to verify the role of these genes in the asthma physiopathology.

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DISTRIBUTION OF HLA-DRB1 ALLELES IN COUNTRIES WITH HIGH TUBERCULOSIS BURDEN (BRAZIL, RUSSIA, INDIA, CHINA AND SOUTH AFRICA): A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction: Tuberculosis (TB) is the worldwide leading cause of death by infectious disease caused by a single agent. Brazil, Russia, India, China and South Africa (BRICS) account for more than half of all TB cases in the world. The only available vaccine, BCG, presents variable efficacy despite its long usage and wide coverage. Epitope based vaccines have been proposed to replace or to booster the effect of early life BCG vaccination, based on specific antigens or portions thereof. Thus, the choice of relevant antigens must take into account their capacity of interaction with the diverse human leucocyte antigen (HLA) molecules found in the target populations. **Methods and Results:** Systematic reviews and metanalyses were performed in each country of BRICS to investigate the most frequent HLA class II alleles, accounting for at least 80% of the population in these countries. MEDLINE database via PubMed was researched between 2013 and 2016 for articles that measured the allele frequencies of HLA-DRB1 in BRICS, resulting in 1,734 analyzed articles of all five countries. After applying inclusion and exclusion criteria, the methodological quality of the articles was evaluated. The presence of publication bias, heterogeneity and frequencies of each HLA-DRB1 allele were evaluated by funnel plots and forest plot. A total of 57 articles involving 192,007 healthy individuals were included in the meta-analysis. **Conclusion:** HLA-DRB1*03, *04, *07, *11, *13 and *15 alleles are the most frequent across the BRICS, varying from a combined estimated frequency of 52% - 80%. HLA-DRB1*01, *08, *09, *10, *12 and *14 are relevant in one or two BRICS populations, achieving more than 80% when combined to the former alleles.

Support: FAPESB and CNPq.

Keywords: Tuberculosis, HLA-DRB1 Epitopes, Vaccine.

VDR VARIANT RS9729 C ALLELE IS NEGATIVELY ASSOCIATED WITH ASTHMA AND VITAMIN D INSUFFICIENCY

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Background: Vitamin D is a secosteroid hormonal with pleiotropic effects. In the immune system causes immunomodulation, reducing inflammatory Th1, Th2, Th17 responses and promoting regulatory profile. Genome-wide studies show a chromosome 12q region, where the vitamin receptor (VDR) is placed, associated with asthma. It is known that *VDR* regulates expression of genes involved in asthma immunopathology, then possibily, variants on this gene may affect asthma. In this study, we have investigated associations between genetic variants in genes of vitamin D pathway and serum levels of 25-hydroxyvitamin D (25(OH)D), atopy, asthma and asthma severity. **Methods:** 25(OH)D was quantified from 968 of 11-17 years old Brazilian teenagers by ELISA. Asthma diagnosis was obtained by using the ISAAC Phase III questionnaire. Specific IgE against aeroallergens was determined by ImmunoCAP; Genotyping was performed using the 2.5 HumanOmni Biochip from Illumina. *In silico* analyses were performed by GTEx. Statistical analyses were performed using PLINK 1.07 and SPSS 22.1. **Results:** After quality control, 104 SNVs in vitamin D pathway genes were included in the analysis typed in 792 individuals. The allele C of variant rs9279 on *VDR*, was associated with lower risk of asthma (OR = 0.66; 95% CI 0.45-0.97) and vitamin D insufficiency (OR = 0.78; 95% CI 0.70-0.96). This variant is in linkage disequilibrium with a synonymous variant rs731236. GTEx analysis showed that genotypes of rs9729 (CC) and rs731236 (CC) were associated with higher expression of VDR receptor in whole blood. **Conclusions:** Genetic variants in vitamin D pathway affect VDR expression, vitamin D serum levels and can impact asthma outcome.

DENND1B HAPLOTYPES ARE ASSOCIATED WITH ASTHMA SEVERITY AND NON-ATOPIC ASTHMA IN BRAZILIAN CHILDREN

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Introduction: About 334 million people in the world suffer from asthma and an estimated 100 million asthma cases are estimated to increase by 2025 worldwide. Asthma is a complex and heterogeneous disease associated with a complex genetic basis involving environmental factors and individual variabilities. The *DENND1B* gene has an important role on T cell receptor (TCR) down-regulation on Th2 cells and studies have shown that mutations or loss of this factor can be associated with increased Th2 responses and asthma. Gene candidate study have recently associated single nucleotide variants (SNVs) in DENND1B gene with asthma in young children. We aimed to determine whether haplotypes of *DENND1B* play any role on asthma severity and non-atopic asthma in Brazilian children. **Methods and Results:** Genotyping was performed using a commercial panel from Illumina (2.5 Human Omni bead chip) in 1,246 participants of SCAALA program (Social Change, Asthma, Allergy in Latin American). The study included 10 SNPs for *DENND1B.* The haplotypes analysis was performed using SNPStats software, adjusted for sex, age, helminth infections and ancestry markers. Results revealed that the haplotypes GGGTTA, AAGCCG and AAGCTA (rs73073636-rs57589685-rs4915551-rs16841893-rs6694441-rs73077640) (OR: 2.04; CI: 1.21-3.45, OR: 2.12; CI: 1.25-3.60, OR: 3.04 CI: 1.20 -7.71, respectively) were associated with an increased risk of asthma severity and the haplotypes AAGACCG and AGGGTTA (rs1421389-rs73073636-rs1421396-rs57589685-rs16841893-rs6694441-rs73077640) (OR: 2.20; CI: 1.17-4.11, OR: 2.07; CI: 1.07-4.01) were associated with an increased risk of non-atopic asthma. **Conclusion:** The genetic polymorphisms of *DENND1B* gene are associated with an increased risk of asthma in a Brazilian population.

Support: FAPESB.

Keywords: DENND1B, polymorphisms, haplotype, asthma

POLYMORPHOSMS IN THE *ST2/IL- 1RL1* GENE ARE ASSOCIATED WITH OBESITY IN A BRAZILIAN POPULATION

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Introduction: Interleukin- 33 (IL- 33) is nuclear cytokine member the IL-1 family expressed in endothelial and epithelial cells, during homeostasis and inflammation. IL-33 works such as an alarm signal released upon cell injury or tissue damage to alert immune cells to express the ST2 receptor (IL-1RL1). IL-33 stimulates the production of cytokines and chemokines in target cells, and Treg cells in the VAT (visceral adipose tissue). The cytokine IL-33 and the ST2/IL-1RL1 receptor is critical for its development of Treg cells in the VAT. Polymorphisms in this receptor are associated with obesity comorbidities such as glucose intolerance. The aim of this study was to investigate if single nucleotide variants (SNVs) in ST2/IL-1RL1 are associated with obesity. **Methods:** The study involved 1,246 participants from the SCAALA (Social Changes of Asthma and Allergy in Latin America) program. Polymorphism in candidate ST2/IL-1RL1 gene was associated with obesity according to the classification of the body mass index (BMI). Genotyping was perf ormed using the Illumina 2.5 Human Omni chip. Logistic regression was used to evaluate the association between variants of ST2/IL-1RL1 with BMI. Analyzes were performed in PLINK 1.9 software, adjusted for age, sex and ancestry markers. **Results:**The **rs3917291(A)** (OR1.81; IC1.19-2.78), **rs3917292 (A)**)(OR0.35; IC0.14-0.90), **rs2287047(A)**(OR0.68; IC0.46-0.99) introns variants, was associated with obesity using dominant model. In the additive model, **rs3917291** (OR1.64; IC1.12-2.41), **rs3917292**(OR0.36; IC0.14-0.89), **rs6750958(G)** (OR1.62; IC1.03-2.52), **rs13394668** (A)(OR 1.61; IC1.03-2.51), **rs12477295(A)**(OR1.393; IC1.00-1.92) introns variants was too associated with obesity **Conclusion:** The polymorphisms **rs3917291, rs6750958, rs13394668, rs12477295** in the ST2/IL-1RL1 gene increase the risk to obesity However, two other polymorphisms **rs2287047** and **rs3917292** are protection related. More studies are important to elucidate how this SNV is involved in obesity.

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