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PROGRAMA DE PÓS-GRADUAÇÃO EM IMUNOLOGIA

XXI ExpoPPGIm
Reunião Anual do Programa de Pós-graduação em Imunologia
RESUMOS
1 a 3 de setembro de 2021

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REVISTA DE CIÊNCIAS MÉDICAS E BIOLÓGICAS

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SUMÁRIO

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APRESENTAÇÃO

O Programa de Pós-graduação em Imunologia (PPGIm) a mais de 30 anos, vem formando recursos humanos de excelência, capacitados para as atividades de ensino e pesquisa em Imunologia e áreas correlatas, muitos já absorvidos por instituições da Bahia e de outros estados. O PPGIm tem realizado reuniões científicas visando difusão do conhecimento científico e integração acadêmica com a graduação e a pós-graduação da própria UFBA e outras IES. A ExpoPPGIm, Reunião Anual do Programa, já se tornou um evento tradicional, que acontece a cada ano, com a primeira edição no ano 2000, constituindo um fórum de integração de profissionais, pesquisadores e jovens cientistas, alunos de graduação e pós-graduação da UFBA e outras IES do Estado da Bahia, do Brasil e de outros Países com interesse no amplo domínio da Imunologia. O objetivo da ExpoPPGIm é divulgar conhecimento científico em Imunologia e áreas correlatas, gerado localmente, na Bahia, no Brasil, e outros países, tendo como público-alvo estudantes de graduação e pós-graduação, pesquisadores da UFBA e outras IES e profissionais da área. Esta XXI Edição da ExpoPPGIm em 2021 foi realizada inteiramente de forma virtual e contou com a participação como palestrantes além de pesquisadores da própria UFBA, pesquisadores vinculados a outras instituições de ensino e pesquisa da Bahia, do Brasil e do exterior, que apresentaram palestras em 6 sessões temáticas, relacionadas às linhas de pesquisa do Programa. Ainda, durante os 3 dias do evento, discentes do Programa apresentaram e discutiram sobre seus projetos de pesquisa em desenvolvimento através de vídeo-pôsteres, distribuídos em 5 sessões, e assim também contribuindo para a integração acadêmica e a difusão do conhecimento científico em Imunologia e seus correlatos.

Profa. Dra. Silvia Lima Costa
Professora Titular de Bioquímica
Coordenadora do Programa de Pós-graduação em Imunologia
Pesquisadora do Laboratório de Neuroquímica e Biologia Celular
Instituto de Ciências da Saúde
Universidade Federal da Bahia

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PROGRAMAÇÃO

01/09/2021
08:30 Abertura Silvia lima Costa, Coordenadora do Programa de Pós-graduação em Imunologia
09:00-10:30 h Conferência Plenária
Roberto José Meyer Nascimento (PPGIm, ICS/UFBA) – Resposta imune ao coronavírus SARS-CoV2
10:30-12:00 Sessão de Vídeo-posters discentes PPGIm – I
Coordenação Silvana Machioro e Alexandre Pinheir.
13:00-15:00 Sessão Temática I – Imunologia e Tecnologia: desafios do SARS-CoV2
Coordenação Simone Macambira e Alex Torres
Bruno Solano (IDOR, IPGM-Fiocruz) – Há espaço para terapia celular no tratamento da COVID-19?
Fabyan Beltrão (UFPB) – Os níveis de hormônio tireoidiano durante a internação hospitalar informam a gravidade da doença e mortalidade em pacientes com COVID-19.
Mona Oliveira (Biolinker) **–** Criando inovações e tecnologia de base e seu papel na pandemia.
15:30-17:30 h Sessão Temática II – Imunogenética e Imunoproteção
Coordenação Ryan Costa e Valdirene Leão
Cinthia Marques (UFBA -VC) Análise exploratória de varredura genômica na infecção por *Helicobacter pylori*
Valdirene Leão (PPGIm, UNEB) – Variantes genéticas da Imunidade Inata e sua relação com Fenótipos de Asma
Helena Mariana Pitangueira (PPGIm) – Estudo de associação genômica ampla (GWAS) de resposta à broncodilatadores.
17:30-18:30 h Conferência Plenária
Alexandre Salgado Basso (UNIFESB/SBI) – Regulação da Resposta Imune Adaptativa pelo Sistema Nervoso Simpático

02/09/2021
08:30 -10:00- Sessão de Vídeo-posters discentes PPGIm – II Nestor Gutierrez e Marcelo Biondaro Góes **10:00-12:00 h C IV – Imunologia das Doenças Infeciosas e Parasitárias** Coordenação Nestor Gutierrez e Marcelo Biondaro Góes) Gessilda Nogueira-Melo (UEM-PR) – Resposta intestinal à infecção crônica por *Leishmania (V) braziliensis* Lucas Carvalho (PPGIm, ICS/UFBA, IPGM-Fiocruz-BA) – Mecanismos patológicos na infecção por *Leishmania braziliensis.* Fabine Passos (UFBA) – Relação entre grupo de bactérias da microbiota intestinal com marcadores clínicos e imunológicos na Doença Pulmonar Obstrutiva Crônica? **13:00-14:30- Sessão de Vídeo-posters discentes PPGIm – III** Coordenação Victor Diogenes Amaral da Silva e Clarissa Schitine **14:30-16:30 h Sessão de Discussão de Vídeo-posters discentes PPGIm-IV** Coordenação Deise Villas Boas de Freitas e Silvia Lima Costa **16:30-18:30 h Sessão Temática Imunologia Aplicada** Coordenação Vitor Antônio Fortuna e Pablo Rafael Silveira Oliveira. Milena Aleluia (UESC) – Aspectos multifatoriais da úlcera de perna na doença falciforme. Pablo Oliveira (PPGIm) – Identificação de marcadores moleculares em doenças infecciosas através de mineração de bases de dados públicas. Brysa Silveira (PPGIm) – Células estromais mesenquimais derivadas de tecido adiposo apresentam potencial angiogênico promissor na cicatrização de feridas de pele.

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03/09/2021

08:30 -10:00- Sessão de Vídeo-posters discentes PPGIm – V

Nestor Gutierrez e Marcelo Biondaro Góes

10:00-12:00 h Sessão Temática V – Imunofarmacologia

Coordenação Juciele Oliveira e Luciana Silva

Margarete Zanardo (FAPESP) – Produtos naturais em estratégias neuroprotetoras e ativação de astrocitária.

Maiara Costa (PPGIm) – Uso de terapias adjuvantes e seus efeitos antitumorais frente ao melanoma experimental.

Jessika Amparo (PPGIm) Caracterização dos mecanismos de ação antiglioma de compostos N-heterocíclicos em células de glioblastoma e em interação com microglia.

13:00-15: 00- Sessão Temática VI – Neuroimunologia

Coordenação Victor Diogenes Amaral da Silva e Clarissa Schitine

Cleide dos Santos Souza (University of Sheefield-UK) – Neurônios sob ataque: o papel dos astrócitos na neurodegeneração.

Thyago Rubens Pires Cardim (UFRJ) – Papel de neutrófilos e de suas redes extracelulares nas doenças amiloidogênicas.

Fillipe Mendes (PPGIm, ICS/UFBA). Neuroinflamação induzida pela endotoxina aminocromo: um novo modelo animal para estudos sobre a Doença de Parkinson.

15:00- 16:30 – Conferência Plenária

Maria Trinida Herrero (Universidade de Murcia -ES) – A teoria priônica e inflamatória de Doença de Parkinson.

16:30-17:00 h Encerramento e Premiação Silvia lima Costa, Coordenadora do Programa de Pós-graduação em Imunologia

ABSTRACTS POSTER SECTIONS

THE GENETIC VARIANT, RS1055659, IN PPARA IS LINKED TO OVERWEIGHT IN BRAZILIAN CHILDREN

Ana Paula Castro Melo; Helena Mariana Pitangueira Teixeira; Raisa Santos Coelho; Neuza Maria Alcantara-Neves; Sheila Maria Alvim de Matos,Silvana D'innocenzo, Rita de Cassia Ribeiro Silva, Maurício Lima Barreto; Ryan dos Santos Costa; Laise C. Pinto; Camila A. Figueiredo.

Introduction: Obesity is a chronic disease with increased risk of asthma, diabetes, hypertension. Obesity has been considered a low-grade inflammatory disease, directly related to insulin resistance and type 2 diabetes mellitus. The peroxisome proliferator activated receptor alpha (PPARα) function has mainly been characterized in the liver, where it regulates the adaptive response to fasting by controlling fatty acid transport, β-oxidation and ketogenesis. PPARα is activated by fibrates, which are therapeutic agents used in the treatment of hypertriglyceridemia. **Objective:** To evaluate the association between polymorphisms in the PPARα gene and obesity in Brazilian children. Methods: The study comprised 1004 children between 5-11 years. Genotyping was done using the Illumina 2.5 Human Omni bead chip. Logistic regression was used to assess the association between BMI (body mass index) and the PPARα gene variations in PLINK 1.9 software. The multivariate analysis was carried out adjusting for sex, age and ancestry markers. **Results and Conclusion**:15.5% (156) of children were overweight. In addition, 59% of overweight children were male and had a mean age of 5 years. There were statistically significant differences for age but not for sex between cases and controls. The rs1055659 was positively associated with overweight using an additive model (T allele, OR: 1.37 95% CI: 1.05-1.78) and in the dominant model (T allele, OR 1:48(1.04-2.04). Thus, the rs1055659 variant in PPARα is linked to a higher risk of obesity in our population. More studies are needed to better understand and elucidate the mechanisms whereby rs1055659 is involved with obesity. **Keywords**: children, overweight, PPARα **Support:** FAPESB.

FLAVONOID AGATHISFLAVONE REPROGRAMS MICROGLIA TOWARDS A NEUROPROTECTIVE INFLAMMATORY PROFILE

Balbino Lino dos Santos, Cleonice Creusa dos Santos, Karina Costa da Silva, Victor Diógenes Amaral da Silva, Maria de Fátima Dias Costa, Arthur Butt, Jorge Mauricio David, Silvia Lima Costa.

In the central nervous system, microglia orchestrate the inflammatory response to diverse insults, including neuroinflammation associated to neurodegenerative diseases (NDD). Microglia recognize damaged cells acquiring a pro-inflammatory cytotoxic profile that can exacerbate brain damage. However, considering microglia plasticity modulation of their inflammatory response to injury may also promote resolution stages of inflammation and tissue regeneration. Agathisflavone, a biflavonoid purified from *Poincianella pyramidalis* (Tul.) has demonstrated anti-inflammatory and neuroprotective properties in vitro models of NDD. Here, we investigated effects of agathisflavona directly in microglial cells submitted to inflammatory damage in view to elucidate mechanisms of neuroprotection associated to modulation of inflammatory response. Microglia were isolated from cortical primary cultures of newborn Wistar rats and were exposed to Escherichia choli lipopolysaccharide (LPS,10 ng/mL) and treated or not with agathisflavone (1-10μM), for 24h.To investigate possible neuroprotective effects of agathisflavona treatment, differentiated PC12 neuronal cells were exposed to the microglia secretoma (MS) derived from cultures in each experimental condition. We observed that inflammatory stimulus with LPS induced the microglia to assume activated cellular state with pro-inflammatory profile characteristic (increased CD68), confirmed by phenotypic changes with more rounded or amoeboid cells. However, when treated with agathisflavone, microglia up-regulated expression of CD206 (anti-inflammatory) and down-regulated CD68 expression, as well presented mainly more branched-like phenotype, in addition to a reduction in the expression of inflammatory mediators IL-6, IL1-b, TNF, NRLP3 and chemokines CCL5 and CCL2, characterizing change to an antiinflammatory state. In the monochlorobimane test, we observed through fluorescence microscopy that there was no reduction in the intracellular GSH content in the DMSO and FAB groups, but there was a marked

spoilage after treatment with BSO and LPS after 24 hours of treatment. In the LPS and FAB groups, there was a slight spoliation of GSH. Moreover, we observe the preservation of neurites and regulation in the expression of βtubulin III and Caspase-3 in PC12 cells exposed to MS derived from agathisflavona and agathisflavona plus LPS treated cultures. Together, these data reinforce the capacity of the flavonoid in reprograming microglia to a neuroprotective anti-inflammatory profile standing out as a promising molecule for the treatment or prevention of NDD. **Keywords:** Neuroprotection, Anti-inflammatory, Flavonoids. **Funding:** CAPES, FAPESB and CNPq.

THE GUT MICROBIOME IN ASTHMATIC INDIVIDUALS FROM SALVADOR, BA

Bianca Sampaio Dotto, Fiuza,Candace Machado de Andrade, Jorley Santos da Silva, Pedro Milet Meirelles, Camila Alexandrina Figueiredo.

Introduction: The Western lifestyle is related to the development of asthma and allergies which could be at least in part to explained by the diet, which is high in fat and sugars and low in fiber, underlying the important role of the environment in the pathogenesis of such diseases. The answer to this relationship may be linked to the molecular mechanisms underlying an axis between gut nutrition and microbiome physiology, since gut microbiota plays several important roles in the development, regulation, and maintenance of healthy immune responses. **Objectives:** To characterize the taxonomic profile of bacteria from the microbiota in stool samples from asthmatic individuals. **Methods:** This project is part of a multicenter study conducted in five different countries. A total of 57 stool samples were collected from each subject (29 samples from asthmatics and 28 samples from nonasthmatics individuals) the bacterial 16S rDNA targeting the V4 region was amplified using PCR and sequenced by Illumina MiSeq high-throughput sequencing. The bioinformatics analysis was conducted using QIIME2 (version 2021.4) and data visualization and analysis using R (version 4.1.0) **Results and Conclusions**: A total of 15 phyla, 25 classes, 39 orders, 75 families, 165 genera and 235 species. All predominant phyla, including Tenericutes, Proteobacteria, Firmicutes, Bacteroidetes and Actinobacteria, were largely consistent in both groups, but different relative abundances could be observed. Alpha diversity showed no significant differences in bacterial richness or diversity between asthmatics and nonasthmatics. Beta diversity analysis was performed by nMDS analysis and ANOSIM test, 01 a 3 de Setembro de 2021 showing significant difference between groups. After filtering the rare taxa in each group, with relative abundance, a total of 10 phyla, 16 classes, 18 orders, 32 families, 47 genera and 59 species remained. Removing unclassified species, 12 species were more abundant in asthmatics and 7 species in non-asthmatics. This study supports the information regarding microbial community differences among asthmatics and non-asthmatics individuals. Additional work should be conducted to better characterize such differences and how they impact on the disease phenotypes and control. **Keywords:** asthma, microbiome, sequencing, gut microbiota **Support:** FAPESB, ERC: European Research Council.

INVOLVEMENT OF THE MTOR GENE AND ITS VARIANTS IN THE SEVERITY OF COVID-19

Bruna Ramos Tosta, Hatilla Santos, Jéssica Francisco de Araújo, Juliana Lopes Rodrigues, Valdirene Leão Carneiro, Soraya Castro Trindade, Helton Estrela Ramos, Camila Alexandrina Figueiredo, Ryan dos Santos Costa.

Introduction: COVID-19, a disease caused by the SARS-CoV-2, has caused thousands of deaths worldwide. In addition to comorbidities, cytokine storm is also associated with disease severity. It is characterized as an exacerbated and uncontrolled systemic inflammatory response, in which there is a large release of cytokines in response to viral infections. The target protein of rapamycin in mammals (mTOR) is a serine threonine kinase and is considered a regulator capable of shaping cellular activation and the inflammatory response of cells of the innate immune response, which is the first line of defense against viral infections. The mTOR pathway plays an important role in this cytokine storm and hyperactivation of this pathway is present in patients with severe COVID-19. Objectives: To investigate the involvement of the mTOR gene in the severity of COVID-19 in the Brazilian population. **Methods**: To form the study population 380 individuals will be recruited (n=130 with mild form and n=250 with severe form of COVID-19), peripheral blood samples will be collected, DNA will be extracted and sequencing will be performed, the polymorphisms in the gene mTOR will be genotyped. The mRNA will be extracted for analysis of gene expression and cytokines relevant to

the study will be measured through serum samples. A genetic database will be built to perform genetic association analysis of polymorphisms with subsequent in silico analysis. **Results and Conclusions**: The peripheral blood samples were collected, and the DNA was extracted and quantified. It is expected that this study will help to understand the influence of genetic variants of the mTOR gene on the severity of COVID19 and that it will contribute to the development of future diagnoses and personalized genetic therapies that bring benefits to the population. **Keywords:** mTOR; COVID-19; severe; polymorphism. **Support**: PPSUS/FAPESB 02/2020 and CAPES 202.

ASC CONDITIONED MEDIUM ACCELERATED WOUND HEALING IN A MURINE MODEL OF SICKLE CELL ANEMIA

Brysa Mariana Dias Silveira; Songeli Menezes Freire; Roberto José Meyer e Vitor Fortuna.

Introduction: Sickle cell anemia is a genetic disease, originating from a mutation in chromosome 11 (replacement of glutamic acid by valine), which gives rise to hemoglobin S. The sickling phenotype of red blood cells hinders its flow through capillaries, causing complications secondary. One of the complications is the formation of chronic leg ulcers (CLUs), which promote a low quality of life and increase the risk of lower limb amputation in patients with sickle cell anemia. The Adipose derived-mesenchymal stromal cells (ASC) are a potential alternative for treatment of CLUs. However, ASCs derived from patients with sickle cell anemia have impaired angiogenic, proliferative and migratory capacity, requiring treatment by heterologous sources. The conditioned medium of ASCs is composed of cytokines, growth factors and bioactive molecules responsible for the repair and regeneration effects of the skin and its use in the treatment of regenerative diseases does not present a risk of rejection to the patient, since CM does not present cellular traces in its composition**. Objective:** Thus, the present study evaluated the effects of normoxia preconditioning on the ASC secretome and analyzed the expression of soluble mediators involved in the tissue repair process. **Methodology:** In this work, ASC were isolated from liposuction samples, cultured for 48 hours and their conditioned medium was administered to wounds created on the back of Townes mice (HbSS). The therapeutic potential was observed through tissue healing model, array analysis and histological assay**. Results:** Our results demonstrated that the ASC secretome preconditioned in normoxia had in its composition the markers of cell regeneration (VEGF, IL8, MCP-1, ANG) and other growth factors involved in angiogenesis and tissue repair. The analysis of the murine tissue healing model showed an improvement in the closure of wounds treated with the conditioned medium, with a reduction in the inflammatory infiltrate and an increase in fibroblasts in the injured area. **Conclusion:** These preliminary data demonstrate that ASC conditioned medium has important regenerative properties for the treatment of skin ulcers in patients with sickle cell anemia. **Support:** FAPESB, CNPq and PIBIC-UFBA. **Keywords:** ASC, chronic ulcers, cell therapy.

IN SILICO CHARACTERIZATION OF A PROTEIN EXCLUSIVE TO CORYNEBACTERIUM PSEUDOTUBERCULOSIS AND EVALUATION OF ITS IMMUNODIAGNOSTIC POTENTIAL

Cintia Sena Carvalho, Leticia Vivas Carvalho, Roberto Meyer, Núbia Seyffert, Thiago Luiz de Paula Castro

Introduction: Corynebacterium pseudotuberculosis is a Gram-positive and facultative anaerobic bacterium known as the etiologic agent of Caseous Lymphadenitis (CLA) in small ruminants. CLA is the main disease caused by this bacterium and harms sheep and goat herds worldwide. Many diagnostic methods have been used to identify sick animals, including the Enzyme-Linked Immunosorbent Assay (ELISA) based on recombinant proteins. Although ELISA is one of the best methods for diagnosing animals with subclinical infections, cross-reactivity issues occur in animals infected with phylogenetically related pathogens. In this context, our group prospected one protein (CP0771) of C. pseudotuberculosis that is exclusive to this species and has potential use in an ELISA-based assay. **Objectives:** This work aims to characterize the properties of protein CP0771 using bioinformatics and proceed with synthesis and immunoreactivity evaluation of the recombinant CP0771. We herein present the preliminary progress of this work, reporting the predicted structural model of CP0771 and prominent epitopes. **Methods:** The three-dimensional (3D) structure of the protein CP0771 was predicted using Robetta server and the TrRosetta method. To achieve a better structure, the 3D model predicted using Robetta was refined using GalaxyRefine. Lastly, ABCPred and Elipro servers were used to predict B-cell linear and conformational epitopes, respectively. **Results and Conclusions:** The initial 3D structure model predicted for protein CP0771 presented 88.4% amino acids in favorable regions according to the Ramachandran plot. This percentage increased to 90.1% following refinement with GalaxyRefine. In addition, sixty

linear epitopes with a score above 0.50 were predicted, sixteen of them with scores above 0.80. Four conformational epitopes with scores ranging from 0.68 to 0.78 were predicted using Elipro. As these results suggest high antigenicity levels for this protein, we plan to express a recombinant CP0771 using Escherichia coli and test its immunoreactivity against sera previously obtained from naturally infected and non-infected sheep and goats. We expect to develop a highly sensitive and specific ELISA for the diagnosis of CLA in sheep and goats. **Keywords:** Caseous lymphadenitis; Immunoinformatics; ELISA **Support:** CAPES, CNPQ.

IL-10 PATHWAY GENE VARIANTS ASSOCIATED WITH A HIGHER RISK FOR ALCOHOL DEPENDENCE IN AN ADMIXED POPULATION

Edson Henrique Bispo Amaral, Gabriela de Sales Guerreiro Britto, Alberto Oliveira Moreira Santos, Daniel Evangelista Santos, Camila Alexandrina Viana de Figueiredo, Mauricio Lima Barreto, Bernardo L. Horta, Ana Lúcia Brunialti Godard, Pablo Rafael Silveira Oliveira.

Introduction: Alcohol dependence (AD) is a multifactorial condition, influenced by environmental and intrinsic factors. Among the intrinsic factors, immune products (such as NFκB and TNF-α) can influence AD as they cause neuronal death by oxidative stress, leading to behavioral changes related to alcohol consumption. Furthermore, family-based studies support the hypothesis of genetic influence on the susceptibility to AD. The most common variants associated with this condition are from genes involved in alcohol's metabolism. Furthermore, other genetic variants have been related to this outcome, including variants in genes that encode molecules with immune function. Despite the body of evidence linking genes from different systems to AD, studies are still needed to identify new factors that may be involved in this condition. **Objetives**: The aim of the present study was to investigate the influence of variants in genes of the IL-10 signaling pathway on the development of AD in an admixed Brazilian cohort. **Material And Methods:** The Alcohol Use Disorders Identification Test (AUDIT) was used to identify individual risk of AD in 3,017 individuals from Pelotas, Brazil. Multivariate logistic regression analyses was done to evaluate the association of Single Nucleotide Variants (SNVs) in genes of the IL-10 pathway (IL10, IL10RB, IL10RA, TYK2 and JAK1) with AD. Fifty thousand phenotype permutations were carried out to obtain empirical p values. **Results:** Six hundred sixty-six subjects were classified as cases (i.e., high risk of alcohol dependence) and 2,351 as controls (i.e., low/moderate risk of alcohol dependence). Males were 46% of the controls and 75% of the cases ($P < 0.05$). As a birth cohort, all individuals had the same age (30 years). The association analyses revealed 20 SNVs that were significantly associated ($Pperm < 0.05$) with AD. From these, the strongest signal is located in an intron of the JAK1 gene (rs7546535, OR=1.28, CI95%=1.12-1.46, Pperm=0.00028). Interestingly, this variant is correlated with JAK1 differential expression in several human tissues. IMPACTS: The identification of immunogenetic mechanisms related to AD can contribute to the development of new therapeutic strategies. Finally, these genetic variants can compose a panel of biological markers to identify individuals at high risk for AD. **Keywords:** Alcohol Dependence; IL-10 pathway; Genetics; Admixed population. **Support:** This project is funded by the Brazilian Ministry of Health (Departamento de Ciência e Tecnologia da Secretaria de Ciência, Tecnologia e Insumos estratégicos, Brazil). Edson Amaral received a doctoral fellowship from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior—Brasil (CAPES, Ministério da Educação, Brazil).

PROTECTIVE EFFECTS OF NICOTINE AGAINST AMINOCHROMEINDUCED CYTOTOXICITY IN GLIAL CELLS: PERSPECTIVES FOR APPLICATION IN PARKINSON'S DISEASE

Érica Novaes Soares; Ana Carla Costa; Cleonice Creusa dos Santos; Maria de Fátima Dias Costa; Yussef TsabI; Rodrigo Portes Ureshino; Silvia Lima Costa; Victor Diógenes Amaral da Silva.

Introduction: Parkinson's disease (PD) is a neurodegenerative disorder that affects brain tissue, especially midbrain dopaminergic neurons. The loss of dopaminergic neurons results in low levels of dopamine and motor symptoms such as dyskinesia, muscle stiffness, posture instability and tremors at rest, which appear after years of degenerative processes and can be preceded by non-motor symptoms such as olfactory and mood disorders. Studies have been

suggested aminochrome as an endogenous neurotoxin responsible for the dopaminergic neuron degeneration in PD. On the other hand, studies have been demonstrated that nicotine protects neuronal cells against aminochrome-toxicity. However, the protective effect of nicotine in glial cells has not yet been studied. **Objective:** The aim of this study was to evaluate the protective effect of nicotine in glial cells in in vitro model of Parkinson's disease induced by aminochrome. **Methodology:** Primary microglia cultures was obtained from neonatal Wistar rats (0-2 days) cortex and mixed primary cultures was obtained from Wistar rat embryos (15 – 16 days) midbrain as described in the approved protocol CEUA 127A/2017 for animal use in experimental procedure. The mixed primary cultures were treated with 25 µM aminochrome and/ or 0.01 µM or 1 µM nicotine for 48 h. Cell viability was performed by propidium iodide test and cell morphology was analyzed by Rosenfeld's stanning. The primary culture of microglia and astrocytes was treated with nicotine at concentrations of 0.0001 µM, 0.001 µM, 0.01 µM, 0.1 µM and 1 µM and aminochrome with 25 and 50 µM, for 48 h. Viability was performed by MTT and phase contrast and Rosenfeld's, lysosomal acidification analyses were reallocated by acridine orange dye, analyzed propidium iodide teste, cell morphology. Results It was observed that 25 µM of aminochrome induced cell death in primary cultures, in addition to 0.01 µM and 0.1 µM of nicotine preventing aminochrome-induced cell damage. It was observed in microglia and astrocytic cultures treated with 0.01 µM and 0.1 nicotine a protective effect against aminochrome-induced cytotoxicity. **Conclusion**: We concluded that nicotine is not cytotoxic at 0.01 µM or 0.1 µM in primary midbrain culture or microglial culture, moreover it protects cells neural cells against aminochrome cytotoxicity. We suggest that more studies must be performed to characterize the mechanism of nicotine action and its effect in glial cells. At the end of the analysis, we expect characterize the effect of nicotine in glial cells and mechanism involved in its protective effect against aminochrome. **Keywords**: Nicotine, aminochrome, midbrain, glial cells. **Support:** FAPESB, CAPES and CNPQ.

COVID-19: EXPRESSION OF SELPG, ITGA4, ARG-1, NOS2 GENES IN TOTAL LEUKOCYTES AND ASSOCIATION WITH DISEASE SEVERITY

Fabiane Silva Reis Góes; Silva, N. N. 1; Gondim, T; Evangelista, G. A. O.; Meyer, R.J.; Trindade, S.C.; Fortuna, V.

Introduction: The immunopathological mechanisms that lead to the severe form of the disease caused by SARS-CoV-2 have not yet been elucidated. So far, more than 4 million deaths have been confirmed worldwide. COVID-19 is most often asymptomatic or with mild symptoms, but around 20% of people develop the severe form of the disease. The severity is attributed to the exacerbation of the host's immune response, with an increase in innate immunity cells, inflammatory mediators in response to viral infection and coagulopathies. Recent studies have related the proteins arginase-1 (ARG-1), nitric oxide synthase (NOS2), α4β1 integrin (ITGA4) and P-selectin glycoprotein ligand-1 (SELPLG) to host immune responses and these probably contribute to a harmful hyperinflammatory state in COVID-19. However, the involvement of these genes in the severity of COVID-19 is still under investigation. **Objective:** To evaluate the expression of genes ARG-1, NOS2, ITGA4 and SELPG in total leukocytes from patients with mild and severe forms of COVID-19. **Method:** Case-control study recruited patients diagnosed by RT-PCR positive for SARS-CoV-2 infection. Patients were grouped into severe outcome – admitted to the ICU, and mild outcome. After isolation of total leukocytes, gene expression was analyzed by qRT-PCR. **Results:** The sample was mostly male (54.6%), with a mean age of 61.7 years in the severe disease group (n=59) and 41.9 years with mild disease (n=59). The proportion of elderly (aged 65 years and over) was higher in the severe group in comparison to the mild group (44.8% vs 10.3%; OR: 7.04; CI: 2.61-18.97; p<0.001). Other factors associated with the prevalence of severe disease were diabetes (OR= 16.26; Cl: 4.56 – 57.95, p<0.001), hypertension (OR= 2.57; Cl: 1.1 – 5.57, p=0.23) and smokers (OR= 20.22; Cl: 4.98 – 82.14, p<0.001). After pairing the samples, cDNAs were prepared and qRT-PCR analysis iscurrently under investigation. **Final Considerations:** In our univariate analysis model,elderly, diabetes, high blood pressure and smoking were factors significantly associated withsevere COVID-19 disease. Studies of immunological biomarkers are needed to understand the pathophysiology of the disease and propose new approaches for discovering prognosticfactors and treating severe COVID-19. **Keywords:** Covid19, leukocytes, ARG1. **Support:** FAPESB, CNPq and PIBIC-UFBA.

C-REACTIVE PROTEIN LEVEL CORRELATION WITH ANXIETY AMONG PATIENTS POST-COVID-19

Fabíola Ramos Jesus, Ana Flávia Reis Prado, Paulo Mateus Madureira Soares Mariano; Marcelo Vincenzo Sarno Filho; Rafael Costa Sarno Neves; Marcel Lima Albuquerque; Margarida Célia Costa Neves, Gyselle Christina Baccan

Introduction: The C-reactive protein (CRP) could be used as an independent factor in predicting the severity of Coronavirus disease 2019 (COVID-19) in the acute phase (Interdiscip. Perspect. Infect. Dis. 2021: 1-5, 2021). Inflammation may contribute to the prevalence of anxiety and depressive symptoms. Post-COVID-19 patients often complain of symptoms like fatigue, dyspnea, anxiety, chest pain, among others. The persistence of symptoms in post-COVID-19 individuals has been assigned to sequelae of organ damage, the persistence of chronic inflammation, the effect of hospitalization, and complications related to comorbidities (Diabetes Metab. Syndr. Clin. Res. Rev. 15: 869-875, 2021). Nevertheless, few studies have been conducted to describe the clinical characteristics and markers of systemic inflammation in patients with persistent symptoms post COVID-19. **Objective:** The aim of this study was to assess the existence of a relationship between anxiety and depression with CRP levels in individuals with persistent symptoms post-COVID-19**. Methods:** This is a retrospective analysis of prospectively collected data in a cohort of subjects with persistent symptoms after acute COVID-19. This study was reviewed and approved by the Research Committee ethics (Protocol 4.389.659). To evaluate anxiety and depression we used Hospital Anxiety and Depression Scale questionnaire. Clinical parameters and CRP were obtained via electronic query of hospital records. The Spearman correlation was used to describe the correlation between the indicators. **Results:** We examined 78 participants that reported persistent symptoms. Thirty-six of them (46.3%) reported persistent symptoms until 24 weeks after initial COVID-19 symptoms with a median age of 55 (IQR: 44-61) years and presence of comorbidities (Systemic Arterial Hypertension =41%; type 2 diabetes=30%; obesity =22%). The median CRP concentration of the sample was 4.5 (IQR: 1.8- 9.2) mg/L. The median scores for anxiety and depression were 10 (IQR: 6-12) and 7 (IQR: 3-11), respectively. The results showed significant positive associations between CRP and anxiety score (r =0.4; p =0.02). No significant correlation was found between the depression score and CRP (r =0.1; p=0.45) Conclusions: Although the research is still under development, it is possible to identify the presence of the relationship between the CRP and symptoms of anxiety in post-COVID-19. **Keywords:** COVID-19, C-reactive protein, anxiety scale.

THE RS11647979 VARIANT AFFECTS BRONCHODILATOR RESPONSE AND DECREASES ADCY9 GENE EXPRESSION IN INDIVIDUALS WITH MILD ASTHMA

Helena M. P. Teixeira; Maria B. R. Santana; Pedro A. S. Santos; Hátilla S. Silva Talita S. Jesus; Bianca S. D. Fiuza; Louise C. Lima; Jéssica F. Araújo; Raísa Coelho; Gabriela P. Pinheiro; Álvaro Cruz b; Ryan S. Costa; Camila A. Figueiredo

Introduction: B2-adrenergic drugs are bronchodilators and comprise the main medication for asthma symptoms relief. Bronchodilator (BD) therapy along with steroids (ICS) is an importantcombination for asthma control and improves quality of life of affected individuals. However, this combination can fail in some individuals considering the multi phenotypes of asthma as well as its genetics complexity. **Aim:** The purpose of this study is to assess whether the rs11647979 variant in the *ADCY9* gene is associated with a lack of response to the β2 adrenergic bronchodilator in individuals with asthma and whether these variants impact the level of *ADCY9* expression. **Methods:** Individuals with asthma (716) from ProAR cohort were genotyped using Illumina's MEGA array. The non-responder outcome was defined by the change in predicted FEV1, after the challenge with salbutamol, less than 12% and/or the 200ml absolute volume variation. The association analysiswas performed using Plink 1.9 software. Blood samples from 95 individuals were collected and peripheral blood mononuclear cells (PBMC) were collected for RNA extraction and *ADCY9* expression. The gene expression analysis was performed using Graph Pad Prism 5. **Results**: The rs11647979 (risk allele: A, OR: 2.29, IC95%: 1.34-3.93) was associated with a lack of response to the bronchodilator in mild asthma, however, no association was found with individuals with severe asthma. In addition, A allele of the rs11647979 decreased *ADCY9* gene expression (p<0.05). CONCLUSION: The *ADCY9* rs11647979 variant affects bronchodilator responses and decreases gene expression in individuals with mild asthma. Perhaps continued exposure to ICS/BD in individuals withsevere asthma can modulate this risk, and therefore resulted in loss of the association. This variant

islocated in a regulatory non-coding region which may explain the functional impact on the response to treatment. Further studies are needed to verify the mechanism whereby this variant affects response to bronchodilator. **Key word:** pharmacogenetics, *ADCY9*, asthma, bronchodilators, salbutamol, SNVs.**Funding:** This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001.This study was financed in part by Programa de Apoio ao Novo Ensino Médio (PRONEM) – FAPESB (Fundação de Amparo à Pesquisa do Estado da Bahia); Edital: 009/2014; Pedido: 8305/2014; Termo de outorga: PNE0003/2014.

ANTIOXIDANT, CYTOTOXIC AND ANTINEUROINFLAMMATORY POTENTIAL IN GLIAL CELLS OF FLAVONOIDS AND DERIVATIVES

Janaina Ribeiro Pereira Soares, Mauricio Moraes Victor, Silvia Lima Costa, Juciele Valéria Ribeiro de Oliveira

Introduction: Neuronal degeneration can be restrained by glial cells through homeostatic control of toxic and inflammatory mechanisms occurring in the central nervous system. Loss of homeostasis leads to increased oxidative stress and inflammation, associated with neurodegenerative diseases (NDD). In this scope, polyphenolic compounds with antioxidant and anti-inflammatory properties, such as flavonoids, are promising candidates for complementary therapies for NDD. **Objectives:** This work carry out an in vitro screening of cytotoxicity and antioxidant mechanisms of flavonoids and synthetic derivatives, associated with the control of the glial inflammatory response. **Methods:** Cell free antioxidant activity of of flavonoids chrysin, apigenin, rhoifolin, hesperidin naringin, naringenin and prenylated synthetic derivatives was determined by free radical scavenging reactions (DPPH). Cytotoxic effects of the compounds (1-100 µM) was determined in human GL15 and rat C6 glioma cells cultures by MTT assay and differential interference contrast (DIC) microscopy. Primary cultures of astrocytes, obtained from Wistar rats (P0-2), were submitted or not to inflammatory damage with LPS (1 µg/mL), after 24 h treated or not with flavonoids and derivatives (10 µM) and, 24 h later, cell phenotype and viability was determined by DIC and MTT, and the levels of the inflammatory mediator nitric oxide (NO) were determined in the culture medium by Griess reaction. The flavonoids hesperidin, apigenin and the diprenylated synthetic derivative of naringenin, at the concentration of 1 µM, showed superior DPPH radical scavenging than the Trolox standard, in addition to maintaining the viability of cells from the primary astrocyte culture. **Results and Conclusions** : These flavonoids reduced the NO levels induced by LPS, an effect also observed after treatment with the monoprenylated synthetic derivative of naringenin. The determination of the antioxidant mechanisms of flavonoids and synthetic derivatives involved in neuroinflammation will contribute to the development of new complementary therapies for NDD. **Keywords:** flavonoids; glial cells; antioxidant, neuroinflammation. **Support:** FAPESB (APP0107/2016; INT 016/2016); CAPES (PGCI Proc. – 88881.117666/2016-01); Nacional Institute for Translational Neuroscience and INCT for Excitotoxicity and Neuroprotection (MCTI/CNPq).

HOST GENETIC FACTORS LINKED TO COVID SUSCEPTIBILITY AND SEVERITY COVID-19

Laiane da Cruz Pena, Milca de Jesus Silva, Yasmim Cristina Ferreira de Almeida, Jéssica Francisco de Araújo, Ryan dos Santos Costa and Camila Alexandrina Figueiredo.

Introduction: The COVID-19 is a disease caused by SARS-COV-2 and its worldwide distribution has culminated in a pandemic decreed by the WHO in March 2020. Different clinical manifestations have been observed varying from asymptomatic to severe phenotypes which require hospitalization and death. Host genetics can explain this variability of manifestations since polymorphisms in genes of clinical importance for the disease can cause changes in the triggered responses. Thus, it is possible that genetic aspects of the host may represent a risk for disease severity in different populations. **Objectives:** This study aims to investigate whether genetic factors are linked to the susceptibility and severity of COVID-19 in a group of case-control patients. Methods: For this, positive and negative patients for COVID-19 (1600 individuals) were sampled from a cross-section carried out at Hospital Universitário Edgar Santos. Phenotypic data were obtained from the patients' clinical records. After collecting peripheral blood, DNA extraction was performed followed by quantification in Nanodrop for further genotyping in QuantStudio 12K. The candidate genes ABO, ACE, ACE2, TMPRSS2 and LZTFL1 were selected based previous published genomic studies. Extracted DNA

was quantified using Nanodrop, and pilot assays were conducted in order to verify sample integrity and optimal DNA concentrations for genotyping. We tested 3 different DNA concentration 5, 10, and 15ng/uL. Results and **Conclusions (Expected Results):** Preliminary results were obtained from data collection and blood sampling for genomic DNA extraction, quantification and piloting for genotyping. The phenotypic characterization analysis showed 192 positive patients for SARS-COv-2, representing 12%. Of the total number of quantified samples, 1281 had a DNA concentration either greater or equal to 50ng while 319 had a concentration below 50ng. After that, plates with uniformized concentration were plated with 5ng/uL of DNA in each well. SNPs genotyping assays are being conducted with the aforementioned genes. Next step is genotype the whole population (1600 individuals) for 5 different SNPs ain 5 differents genes linked to COVID-19. We believe our work will contribute to a better understanding of how genetic factors may be associated with the higher risk for susceptibility/severity of COVID-19 in an admixture population from Brazil. **Keywords:** Polymorphisms, COVID-19, SARS-COV-2, genotyping. **Support:** CAPES.

FUNCTIONAL ANALYSIS OF RUTIN FLAVONOID IN INTESTINAL SEGMENTS (ILEUM AND COLON) IN EXPERIMENTAL MODEL OF PARKINSON'S DISEASE

Livia Bacelar de Jesus, Annyta Fernandes Frota, Fillipe Mendes Araújo; Rafael Leonne, Cruz de Jesus, Victor Diogenes Amaral, Darizy Flavia Silva, Marcelo Biondaro Goes, Gyselle Chrystina Baccan, Silvia Lima Costa.

Introduction: The enteric nervous system (ENS) is a complex neural network embeddedin the gut wall that orchestrates the reflex behaviors of the intestine performing an essential role in regulating many gastrointestinal functions including motility and fluid secretion. The involvement of ENS has been shown to be important in the neurodegenerative process underlying Parkinson's disease (PD). Studies have demonstrated that natural substances, such as flavonoids, can aid bowel function in PDpatients, lower the risk for the development of the disease. The flavonoid rutin, present in abundance in seeds of the Brazilian plant Dimorphandra mollis, has been demonstrated neuroprotective and anti-neuroinflammatory effects in in vitro models of PD. **Objective** The preset study evaluate the effect of rutin on gastrointestinal function ofrats in a PD model**. Materials and methods**: For this male adult Wistar rats submitted to unilateral nigrostriatal injection of 6 hydroxidopamine (21µg/kg, PD group) or saline (Control group) were submitted or not to oral treatment daily with rutin (10mg/Kg) for 14 days. The induction of PD was validated by administration of apomorphine (3mg/kg). The gastrointestinal transit before euthanasia was evaluated by gavage of Carmine Red (6%). On the 15th day the ileum and colon segments were collected and processed for hematoxylin/eosin staning. Tissue contraction was determined with intestine fragments stimulated with carbacol and nitric oxide donor (10^{-10} – 10^{-4}M), in addition to KCl (80mM).**Result:** It was observed that parkinsonian animals had a lower content of free water in feces when compared to the control animals and this behavior was reversed in animalstreated with rutin (20%, $p<0,05$), fecal production and gastrointestinal transit were increased, besides colon contractility. The combined treatment of rutin and 6OHDA increases ileal smooth muscle reactivity to muscarinic activation and appears to reducerelaxation through the signaling pathway of nitric oxide donors ($p<0,01$). Rutin treated animals also presented an increase in the cell body of paneth cells, although rutin treatment does not change the amount of goblet cells in rat ileum and colon segments. **Conclusion**: The results show that treatment with flavonoid rutin seems to improve gastrointestinal function and increase contractility of the ileal and colonic segment in parkinsonian rats, in addition to demonstrating participation of innate immunity with paneth cells.

VARIANTS IN THE GATA3 GENE ARE ASSOCIATED WITH RISK FOR ASTHMA AND ATOPY IN A BRAZILIAN POPULATION

Louise C. de Lima, Álvaro A. Cruz, Ryan dos S. Costa, Raísa S. Coelho, Helena Mariana P. Teixeira, Camila A. V. Figueiredo, Valdirene L. Carneiro

Asthma is characterized as multifactorial morbidity, with high prevalence and worldwide relevance. It is a common chronic inflammatory airway disease that affects thousands of people in different countries and is associated with high mortality. The T cell-specifictrans-acting transcription factor (GATA-3) is related to type 2 asthma phenotypes. This transcription factor is responsible for the activation of innate lymphoid type 2 (ILC2) andhelper T cells (Th2), resulting

in the production of IL-4, IL-5, and IL-13 by these cells andconsequent activation and migration of inflammatory cells from the circulation to the airways, in addition to hyperresponsiveness and bronchial remodeling. This work aims to evaluate the association of *GATA3* gene variants with asthma and atopy markers. Thisis a case-control study composed of patients from the Asthma and Allergic Rhinitis Control Program in Bahia (ProAR), who are over 18 years old and reside in Salvador-BA.These patients were divided into three groups (controls, mild asthma, and severe asthma) diagnosed with asthma according to the Global Initiative for Asthma (GINA). The genotyping was performed using the Illumina Multi-Ethnic Genotyping Array (MEGA) chip. The dominant and additive logistic regression models were used for association analysis, using the Plink 1.9 program, and comparisons between genetic groups were analyzed using the GraphPad Prism 6 program. The A allele of rs263423 and the G allele of rs263424 were significantly associated with the risk of asthma (OR: 1.24, OR: 1.30, respectively) and the allele The T of rs406103 and the A allele of rs11255501 were significantly associated with the risk of atopy (OR: 1.32, OR: 2.83, respectively). The SNVs of this gene also showed significant differences between their genotypes for peripheral blood eosinophil count (rs11255501) and for the cytokine eotaxin (rs406103), p <0.05. These data demonstrate that the *GATA3* gene is an important candidate for further studies involving the Brazilian population, with a large part of its population of African descent. However, functional studies are needed to elucidate the mechanisms involved in these results, such as the analysis of gene expression. **Keywords:** Variants, Asthma, GATA-3.

EVALUATION OF THE ANTI-INFLAMMATORY EFFECT OF ECHINACEA PURPUREA ON HISTOMORPHOMETRY OF COLONIC MUCOSA OF TOXOPLASMA GONDII INFECTED RATS

Luana Araújo Mercês, L. A.; Santos, D., Santos, T. T., Pastre, M. J., Góis, M. B.

Introduction and objectives: Currently, toxoplasmosis is treated with the chemotherapeutic agents pyrimethamine and sulfadiazine, which inhibit enzymes essential for *Toxoplasma gondii* DNA synthesis. However, overuse has resulted in the selection of resistant strains of the parasite. Therefore, the aim of this study is to investigate the effects of a herbal drug on the colonic mucosa of rats infected with *T. gondii*. **Methods:** The experimental protocol was approved by CEUA-UEM (7633021018). Twenty-four *Rattus norvegicus* were divided into a control group (GC), an infected and untreated group (GI-NT), a treated control group (GC-EP), and an infected and treated group (GI-EP) (n=6). The infected groups were orally inoculated with 500 sporulated oocysts of *T. gondii* (RH strain). Rats in the GC-EP and GI -EP groups were treated orally with 100 mg/kg *Echinaceapurpurea* daily for 30 days before and after the inoculation date of the infected groups. Sixtydays after infection, the rats were euthanized, and the colon was removed. One-centimeter-long segments of the colon were fixed in buffered paraformaldehyde (4%) for 4 h. The segments were then dehydrated, diaphanized, and embedded in paraffin to obtain semi-serial cross-sections of 4 μm, which were stained with hematoxylin and eosin. The thickness (μm) of the mucosa was determined under 20× magnification. Sixty-four measurements were taken over the entire circumference of the colon of each rat. Histomorphometric analysis was performed using images captured with a digital camera connected to a light microscope and Image-Pro Plus software (Media Cybernetics, USA). **Results and conclusions:** Histomorphometric analysis showed atrophy of colonic mucosa in GCI-NT (267.1±114.8), GC-E100 (296.8±112.7) and GI-E100 (289.1±78.4) groups compared to control GC (328.7±72.2) group (p<0.05). Toxoplasmic infection caused histomorphometric changes in colon mucosa. In turn, treatment with *E. purpurea* failed to reverse the atrophy of the colonic mucosa caused by the infection. **Keywords:** Toxoplasmosis, RH strain, herbal drug.**Support:** Fundação de Amparo à Pesquisa do Estado da Bahia-FAPESB.

MORPHOLOGICAL CHANGES IN GLIAL CELLS INDUCED BY LPS INFLAMMATORY STIMULI IN A NEW PRIMARY CULTURE OF CEREBELLAR CELLS

Lúcia Santana, L. F; Santos, C. C; Ferreira, R. S; Almeida, A. M. A. N; De Castro, M. V. L; Franchi, M. S.; Andrade, G. B; Da Silva, T. M; Costa, S. 1, and Silva, V. D. A

Introduction: The communication between glial cells and neurons modulates the pattern of neuroinflammation. Astrocytes and microglia are the main immune effector cells in the central nervous system (CNS). In CNS injury, they become activated and acquire pro-inflammatory or regulatory response profiles. Therefore, different in vitro models have been proposed to study glial cells on neuroinflammation. Classic cerebellum culture models have been used. However, they do not provide information about neurons and oligodendrocyte precursor cells (OPC) yield. **Objectives:** The aim of this study was to develop a primary culture of cerebellar cells protocol to obtain a higher yield of neurons; characterize the presence of OPC and study morphological changes in glial cells on inflammatory stimulus.

Methods: Therefore, primary cultures of cerebellar cells were cultured in growth factors before, primary of cerebellar cells were cultured in growth factors (bFGF, insulin) supplemented DMEM F12 medium and autocrine conditioned medium. Subsequently, they were exposed to 1 ug/mL lipopolysaccharide (LPS) for 24 hours and analyzed by immunostaining for markers of neurons (β-TUB III), astrocytes (GFAP / ALDH1 L1), microglia (Iba1), and OPCs (Olig2). Results and Discussion: The new protocol provided a proportion of 58% neurons, 27% astrocytes, 6% microglia, and 8% OPC and preserved the pattern of glial response for LPS. This set of data has not previously been described with classical primary culture models of cerebellum. **Conclusion**: Thus, we suggest the application of this new protocol for primary culture of cerebellar cells as a valuable tool to study the effect of inflammatory astroglial and microglial response in neurons and OPC. **Keywords:** Neuroinflammation, glia, cerebellum, in vitro. Support: FAPESB, CAPES, CNPq.

EVALUATION OF GENETIC MARKERS PANELS PREDICTORS OF BRONCHODILATOR RESPONSE IN PATIENTS WITH ASTHMA BY USING MACHINE LEARNING

Luciano Gama da Silva Gomes; Helena M. P. Teixeira; Gabriela P. Pinheiro; Álvaro A. S. Cruz; Ryan S. Costa; Camila A. V. Figueiredo

Introduction: Asthma is a phenotypically heterogeneous disease. Therefore, it is laborious to form and understand certain phenotypic and genotypic patterns. Bronchodilator therapy is the mainstay of asthma treatment, however, there are patients who do not respond adequately to treatment. Predicting treatment failure can optimize therapeutic patient control. Has been proposed the use of genetic variants as predictive biomarkers of complex outcomes, such as treatment response. **Objective:** To evaluate different methods to select genetic markers for the construction of predictive models of bronchodilator response in patients with asthma by using Machine Learning**. Material and Methods:** 450 asthmatic patients were selected from the PROAR cohort, with 203 responders to bronchodilators and 247 poor responders. Were included 50,329 SNVs previously associated in GWAS with bronchodilator response. Variable selections were made using three different methods: (1) selection of the first hundred associated genetic variants in the GWAS from our population, according to their respective p-values; (2) selection using the Boruta algorithm; (3) selection using LASSO regression. For the prediction, the Naive Bayes algorithm was used. All analyzes were performed in R, using e1071, Boruta, glmnet, caret and pROC packages. Results and Discussion: A panel containing 63 variants was defined by Boruta; and within 15 variants by LASSO. The model using 50,329 variables had a test accuracy of 99.25% (sensitivity of 100.00% and specificity of 98.33%); the model made by the 100 top SNVs obtained an accuracy of 88.06% (89.19% and 86.67%); the model generated by the variables selected by Boruta presented an accuracy of 89.55% (90.54% and 88.33%); and, the model generated by the SNVs selected by LASSO regression presented an accuracy of 76.87% (79.73% and 73.33%). Respectively, the area under the curve was: 0.992, 0.953, 0.940 and 0.859. Thus, it was possible to observe that the Naive Bayes classifier is powerful, and the selected variables can influence the prediction power. However, the computational burden and optimization of model generation must be considered. The selection of a reduced number of genetic markers offered high accuracy for the prediction of bronchodilator response, which may enable its implementation in clinical practice. **Conclusion:** Models generated by selection of genetic variables can assume high predictive accuracy of response to bronchodilator use from asthma patients. **Keyword:** bronchodilator, SNV, Machine Learning, prediction. **Support**: CNPq.PRONEM/FAPESB.

GENETIC VARIANTS IN GENES THAT EXPRESS INFLAMMASOME-FORMING PROTEINS ARE ASSOCIATED WITH PERIODONTAL DISEASE

Marcia Otto Barrientos, Helena M. P. Teixeira, Soraya Castro Trindade, Isaac Suzart Gomes-Filho, Álvaro A. S. Cruz, Ryan dos Santos Costa, Camila A. Figueiredo, Tatiane de Oliveira Teixeira Muniz Carletto

Introduction: Inflammasomes are important cytosolic signal recognizers whether microbial or not. They are multimolecular compounds linked to proteins of the innate immune system. The responses generated by an inflammasome depend on the origin of its activation, which can be pro-inflammatory or antiinflammatory. Among the inflammasomes

components described in the literature, IFI16 and AIM2 has been associated with periodontal disease since the advent of GWAS. IFI16 promotes the formation of the AIM2 inflammasome but also antagonizes its actions, thus modulating the inflammatory process. **Objective:** To investigate the association of the genetic variants in IFI16 and AMI2 with the presence of periodontal disease in a population of Salvador/Bahia/Brazil. **Methods:** The study involved 506 adults individuals in the Program of Control of Asthma and Allergic Rhinitis of Bahia (ProAR) that were classified for the presence (n=117) or absence (n=389) of periodontal disease. Genotyping was performed using the Illumina Infinium kit Multi-Ethnic AMR/AFR-8. Statistical analysis used PLINK 1.9 software, logistic regression in three models – additive, dominant and recessive, adjust for age, obesity, mouth breathing, flossing, asthma and the principal component of ancestry, considering the HardyWeinberg equilibrium deviation (HWE0.01). **Results and Discussion**: The allele A in rs75985579 of IF16 was associated with predisposition with periodontal disease in additive and dominant genetic model (OR=2.65, 95%CI=1.25-5.60, p=0.011, p-perm=0.007; OR=2.56 95%CI=1.13-5.81, p=0.024, p-perm=0.017, respectively). The allele G in rs76457189 of AIM2 was associated with protection in additive and dominant genetic model, both with the same result (OR=0.21; 95%IC=0.05-0.94, p=0.041, p-perm=0.022). The bacterial action on the periodontium is a important but not decisive factor for the development of periodontitis. Homeostatic mechanisms deregulated by genetic variants in the genes studied can induce the inadequate formation of inflammasomes, as well as an unexpected inflammatory response. **Conclusion:** These results suggest that SNVs on the IFI16 predisposes the individual to periodontal disease at levels 150% higher than those who do not have it. However, genetic variants in the AIM2 gene protects against the development of periodontitis by approximately 80%. Further studies are needed to replicate our findings and investigate the functional impact of these variants. **Keywords:** Polymorphism, IFI16, AIM2, periodontal disease. **Supports**: CAPES, UFBA.

INFLUENCE OF TRYPANOSOMA CRUZI COINFECTION ON THE IMMUNE RESPONSE AND CLINICAL OUTCOME OF PATIENTS WITH CUTANEOUS LEISHMANIASIS

Mônica Sousa Pita, Rúbia Suely Santana Costa, Andréa Santos Magalhães, Lucas Pedreira de Carvalho

Introduction. In several areas of Latin America, the geographical distribution of cutaneous Leishmaniasis (CL) overlaps with areas of Chagas disease transmission ranging from 12 to 70% of patients with clinical symptoms for leishmaniasis. A higher T cell differentiation profile has been observed in patients with CL and mucosal leishmaniasis (ML) infected with Trypanossoma cruzi compared to patients only infected with leishmania (Bracco, María M. de Elizalde de. 2016). **Objectives.** To assess whether the immune response of patients with CL caused by L. braziliensis and co-infected by T. cruzi is associated with the clinical outcome. Material and **Methods.** A case-control study in which patients with CL caused by L. braziliensis, living in the endemic area of Corte de Pedra, Bahia, were selected. Two hundred cutaneous leishmaniasis patients serum were evaluated chimeric Trypanossoma cruzi specific proteins to detect co-infection with Chagas disease by the ELISA technique. **Results and Discussion** Twenty subjects (10%) were co-infected and showing higher antileishmania and anti-T.cruzi antibody titers compared to the twenty patients infected with Leishmania alone. In addition, IgG1 and IgG3 subclass titers were higher in the co-infected group (p = 0.025). Fourteen (70%) of the co-infected individuals failed antimonial therapy, while in the group of patients only with cutaneous leishmaniose, just 35% failed to treatment, suggesting that T. cruzi infection may interfere with time to cure for the infection caused by L. braziliensis. **Conclusions.**These results indicate that co-infection can interfere with the immune response and clinical evolution of the individual to Leishmania infection. **Key words:** Leishmaniasis, Chagas Disease, coinfection, Immune Response **Support:** National Institute of Science and Technology – Tropical diseases (INCT-DT).

STUDY OF THE MOLECULAR MECHANISMS ASSOCIATED WITH ANTIGLIOMA AND IMMUNOMODULATORY EFFECTS OF FLAVONOIDS RELATED TO INTERACTION WITH AHR

Monique Reis de Santana, Ravena Pereira do Nascimento, David Gilot, Silvia Lima Costa

Introduction: The role of natural flavonoids in cancer prevention has long been described for several types of cancer. Given the therapeutic potential of flavonoids and their antiinflammatory activity in human glioma cells these drugs

have encouraged studies in alternative therapy for malignant gliomas. BRAF-V600E mutations were identified as a marker for a small subset of infiltrating gliomas in adults and appears to be related to chemo and immunoresistance and poor prognosis. It has recently been shown that many mechanisms potentially involved in the tumor recurrence of gliomas have been associated to increased expression of BRAFi resistance genes. Increasing evidence indicates that the transcription factor aryl hydrocarbon receptor (AhR) is constitutively activated in tumor cells, promoting the differentiation and increased expression of BRAFi resistance genes, putting AhR antagonism as a target in cancer chemotherapy. In this context, the characterization of the molecular mechanisms of flavonoids featuring a possible antagonistic effect on AhR and its role in chemosensitivity, will contribute to sustain their application as adjuvant for glioma treatments. **Objectives:** This study aims to investigate the action of flavonoids in the modulation of molecular targets such as AhR and its relationship with their antitumor and immunomodulatory potential. Material and **Methods:** Natural flavonoids, whose anti-glioma effects have already been demonstrated, such as apigenin, rutin, naringin, naringenin, 7-oprenilnaringenin and chrysin were tested as AhR antagonists using the induction of CYP1A1-mediated EROD activity assay in MCF7 cells, as a marker of Ah-responsiveness, and relationship with cell viability was determined by MTT reduction test. **Results:** CYP1A1- mediated EROD activity assay of apigenin, rutin and chrysin showed to be powerful antagonists of canonical AhR activity. Such regulations showed to be dose-dependent. **Keywords:** glioma; flavonoids; AhR, immunomodulation **Support**: FAPESB (APP0107/2016; INT 016/2016); CAPES (PGCI Proc. – 88881.117666/2016-01); Nacional Institute for Translational Neuroscience and INCT for Excitotoxicity and Neuroprotection (MCTI/CNPq).

ASSOCIATION OF TYPE 1 INTERFERON, RECEPTORS INFAR1/2, INTERLEUKIN 17A AND ENDOGENOUS RETROVIRUS (HERV-K AND HERV-W) EXPRESSION IN LEUCOCYTES WITH COVID-19 SEVERITY

Nívia Nonato Silva; Reis-Góes, F.S, Gondim, T., Figueiredo, R. G.; Meyer, R.J. Trindade, S.C., Fortuna, V.

Introduction: COVID-19, an acute respiratory disease caused by the new SARS-CoV-2 coronavirus, ranges from asymptomatic to severe symptoms in patients. It is possible that factors involved in virus- host interaction may play an important role in defining the severity of the disease. Impaired signalingof type I IFN (IFN-1 and its receptors) associated with dysregulated expression of the cytokine IL-17A likely contributes to a harmful hyperinflammatory state in COVID-19. Human endogenous retroviruses (HERVs), remnants of ancestral viral genomic insertions, are reactivated in response to infectious agents, modulate the innate immune response and lead to various immunopathological effects, but their contribution to COVID-19 severity is still under investigation. **Objective:** To evaluate the expression of IFN-1 and its receptors INFAR1/2, IL-17A, as well as HERV-K and HERV-W in patients with mild or severe COVID-19. **Methods:** In this case-control study, patients with positive PCR for SARS-CoV-2 were included, and grouped in mild or severe disease. After isolation of total leukocytes,gene expression was analyzed by qRT-PCR. **Preliminary Results:** Among the sample studied, there was a preponderance of males (53. 4%). The mean age for the severe group was 61.7 y and 41.9 yfor the mild group. The proportion of elderly people (>= 65 years) was higher in the severe group in comparison to the mild group (44.8% vs 10.3%; OR: 7.04; CI: 2.61-18.97; p<0.001). Other factors associated with severe disease were hypertension (OR= 2.57; Cl: 1.1 – 5.57, p=0.23), diabetes (OR= 16.26; Cl: 4.56 – 57.95, p<0.001) and smokers (OR= 20.22; Cl: 4.98 – 82.14, p<0.001). After pairing the samples, cDNAs were prepared and qRT-PCR analysis is currently under execution. **Final Considerations:** In view of the current pandemic scenario, our analysis model indicates that the segment most affected by COVID-19 comprises the male, elderly, with hypertension, diabetes and smokers. Therefore, knowledge of immunological markers related to severity is essential to propose aprognosis and new forms of treatment for cases of severe COVID-19. **Keywords**: COVID-19. HERV. Interferon type 1. **Support:** FAPESB, CNPq and PIBIC-UFBA.

ASSOCIATION BETWEEN VARIANTS IN THE GENES OF METALLOPROTEINASES 1, 8, 9 AND PERIODONTITIS

Patrícia M. de Miranda, Rebeca Pereira Bulhosa Santos, Tatiane de Oliveira Teixeira Muniz Carletto, Camila Alexandrina Viana de Figueiredo, Michelle Miranda Lopes Falcão, Soraya Castro Trindade

Introduction: Periodontitis is a chronic inflammatory disease characterized by the destruction of supporting tissues of teeth and triggered by the host's immune response to the presence of a dysbiotic subgingival biofilm. Metalloproteinases (MMPs) are proteolytic enzymes involved in the inflammatory process in periodontal disease, and MMPs 1, 8 and 9 seems to be the main enzymes related to periodontal destruction. In addition to degrading the extracellular matrix they are able to cleave several signaling molecules such as cytokines, chemokines and growth factors involved in the regulation of their biological function and/or bioavailability during periodontitis. The increased frequency of some MMP variants of single nucleotides (SNVs) in individuals with periodontitis in distinct populations suggests that polymorphisms in MMP genes may alter protein expression, predisposing to the development of periodontitis. **Objective:** To investigate the association of genotypic frequency and allelic frequency of SNVs of MMPs with the occurrence and severity of periodontitis. **Material and methods:** This is a cross-sectional study nested in a case-control study, carried out with a blood sample from adults and individuals with periodontitis, recruited at the Health Center of the Asthma Control Program of Bahia (ProAR). After genomic DNA extraction, SNV genotyping was performed using qPCR. The association of allelic and genotypic frequencies of SNVs of MPPs with periodontitis is under cerification through the bivariate and multivariate analysis. Statistical analysis is being performed in SPSS and PLINK statistical programs. Expected results: It is expected to find a positive association between the functional polymorphisms of the genes of metalloproteinases 1, 8 and 9 with the occurrence and severity of periodontitis. **Keywords:** Metalloproteinases, Single Nucleotide Polymorphism and Periodontitis Acknowledgment: CAPES, LABIMUNO (ICS-UFBA),PPGIm (ICS-UFBA).

ADRB2 GENE VARIANTS INFLUENCE THE ACUTE B2-ADRENERGIC RESPONSE AND ASTHMA CONTROL IN A BRAZILIAN POPULATION.

Pedro Augusto S. dos Santos, Helena Mariana Pitangueira, Luciano Gama da Silva Gomes, Hatilla Santos, Almirane Lima de Oliveira, Gustavo Nunes de Oliveira Costa, Gabriela Pimentel, Álvaro A. Cruz, Camila Alexandrina Figueiredo,Ryan dos S. Costa

Introduction: Asthma is a chronic inflammatory disease of the lower airways linked to both environmental and genetic triggers. Agonists that act on the β2- adrenergic receptor, encoded by the ADRB2 gene, are the main line of bronchodilation used in this condition in case of both symptoms control and also exacerbations. However, the literature describes individual differences in response to such drugs which are often related to genetic polymorphisms in ADRB2 gene, however, controversial results have been described across populations. **Objectives:** To evaluate the association of variants in ADRB2 and the acute response to bronchodilators (reversibility) and in asthma control in an urban population from Brazil. Material and Methods: The study was carried out by analyzing the genotyping data of 813 individuals, of which 401 were diagnosed with severe asthma and 412 mild or moderate asthma recruited by the Program for the Control of Asthma in Bahia (ProAR). **Results and Discussion:** The longitudinal analysis of the spirometry data of individuals with severe asthma, revealed the association of the rs1042713, rs1042714 and rs1042717 variants with the change in the response profile to short-acting bronchodilators throughout time compared to the expected response. Also, it was identified that the G allele of the rs1042714 variant and the A allele of the rs1042717 variant were associated with uncontrolled asthma despite regular treatment with LABA combined with ICS, in the severe asthma group. From the analysis of genotypic sets, it was observed that individuals within the severe asthma group who had a set of G46 / G79 / A252 alleles developed mainly uncontrolled asthma. Conclusion: The elaboration of a panel with the studied variants, considering the response variations over age, could contribute as a complementary tool in the therapeutic decision, representing an aspect of potential importance for future studies in the field of personalized medicine. **Keywords:** polymorphism, spirometry, ADRB2, reversibility, asthma control. **Support:** This study was supported by the funding institutions and programs CAPES, FAPESB, CNPq and PRONEM.

ZIKA VIRUS SINGULAR PEPTIDE PRODUCTION FOR THE DEVELOPMENT OF SEROLOGICAL IMMUNOASSAYS AND EVALUATION OF IMMUNE RESPONSE

Rafael Ribeiro Mota Souza, Isabela Brandão Peixoto, Rejane Hughes Carvalho, Gubio Soares Campos, Silvana Beutinger Marchioro, Roberto José Meyer Nascimento, Silvia Ines Sardi

Introduction: The rapid spread of Zika virus (ZIKV) in endemic regions where other Flaviviruses have already been established, such as Dengue Virus (DENV), has led to difficulties in accurately diagnosing the infectious agent. Both Flaviviruses present very similar acute symptomatic conditions and high similarity among their viral proteins, which leads to serology cross-reactions between Zika and Dengue, producing false positive results. In addition, studies have demonstrated that antibody-dependent enhancement also increases viremia due to the cross-reaction between the tests. **Objectives:** Based on the demand for more specific antigens, the present project aims to produce non cross-reactive ZIKV antigens for immunodiagnostic. **Material and Methods:** Unique epitopes were identified using bioinformatic tools to analyse amino acids conservancy, similarity, and antigenicity. We used BL21 Star to express antigens designed to present specific epitopes of ZIKV and evaluated their reactivity performing immunoassays. **Results and Discussion:** Bioinformatic analysis highlighted unique epitopes of ZIKV, from which we selected the region 146-182 of E protein, and 220-352 of NS1. Evaluating the sensitivity and specificity of the recombinant in tandem E protein (Tan_E), by Dot Blot we observed a significant difference between ZIKV and DENV IgG+ sera, agast induced bacterias, but not in purified protein. Also, we did not observe significance by ELISA and Western blot, which suggest that the chosen region, despite predictions and indications, is not a sensitive region. Future experiments include the expression of parcial NS1 of ZIKV and the evaluation of it's sensitivity and specificity**. Conclusion:** Overall, the investigation of the ZIKV epitopes based on previous bioinformatic analysis could lead to the elaboration of new tools for immunodiagnosis, providing a more accurate strategy to the surveillance of ZIKV.

RS6966536 VARIANT IN THE LEP GENE IS ASSOCIATED WITH ASTHMA SEVERITY AND LACK OF DISEASE CONTROL IN OBESITY-RELATED ASTHMA

Raísa Coelho, Carla Rodrigues, Ana Paula Melo, Helena Teixeira, Louise Lima, Jamille Fernandes, Gustavo Costa, Gabriela Pinheiro, Adelmir Machado, Álvaro Cruz, Camila A Figueiredo, Ryan Costa.

Introduction: Asthma and obesity are chronic diseases with increasing prevalence that, in addition to environmental and genetic factors, have inflammation as a common link. In this sense, cytokines secreted by adipose tissue cells (adipocytes and macrophages) with receptors expressed in the lung are pointed at the link between the immune regulation involved in the pathogenesis of both diseases. Variations in the gene responsible for the protein Leptin (LEP) have been associated with unbalanced LEP serum levels and consequent metabolic dysfunction that impacts asthma severity. **Objectives:** the aim of this study is to investigate the association between LEP gene variants with asthma outcomes in a Brazilian population as well as identify if overweight affect this association. **Methods:** The study involved 1085 individuals, followed by ProAR (Program for Control of Asthma and Allergic Rhinitis of Bahia). Asthma and disease severity were defined according to GINA and overweight/obesity was defined by BMI, according to WHO. Genotyping was performed using Illumina Infinium kit Multi-Ethnic AMR / AFR-8. Logistic regression was performed to identify associations between variants in the studied gene with asthma severity, stratifying or not the population by BMI. **Results and Conclusions:** The rs6966536 (G allele) was positively associated with asthma severity (OR 2.36; CI 1.19-4.68) in the additive model and lack of asthma control despite regular use of corticosteroids and bronchodilators (OR 2.04; CI 1.06 3.90) in subjects with overweight, while the associations were not observed non-overweight individuals. Our results demonstrate the modifying effect of overweight on the observed association between variants in the LEP gene and asthma severity and control. Functional studies are needed to clarify the inflammatory hypothesis of such associations. **Keywords:** Asthma. Severity. Obesity. Leptin. Genetic. **Support:** FAPESB.

EVALUATION OF THE GENE EXPRESSION OF OSTEOBLASTS PRODUCED IN SYNTHETIC MATRIX

Rebeca Pereira Bulhosa Santos, Patrícia Mares de Miranda, Michelle Miranda Lopes Falcão, Lucas Novaes Teixeira, Viviane Almeida Sarmento, Soraya Castro Trindade

Introduction: Some orofacial injuries are related to loss of bone continuity, and, consequently, to structural and functional damage that impair the life quality. The production of biological tissues from cell cultures is suggested as an auxiliary strategy for orofacial reconstructive surgeries, however, the effectiveness of the technique depends on a support structure that guides the formation of functional tissues according to the receptor bed. **Objective:** To investigate the gene expression signature and functionality of osteoblastic cells (SAOS-2) cultured on rigid matrices produced with three-dimensional printer. Material and Methods: The functionality of osteoblasts cultured on poly-lactic acid (PLA), acrylonitrilebutadiene-styrene (ABS M30i) and PC-ISO polycarbonate scaffolds will be evaluated by Array Real time PCR system to determine the expression of 84 genes related to osteoblastic differentiation, bone mineralization, ossification, growth factors and transcription factors involved in inflammation and scarring. **Expected Results**: It is expected to determine the protocol for the production of viable osteogenic tissue for the repair of facial bone defects, contributing to the development and establishment of tissue recovery materials. **Keywords:** Gene expression.; Osteoblasts; scaffolds and tissue engineering. **Support:** Capes, Federal University of Bahia and State University of Feira de Santana.

PRETREATMENT LEVEL OF HEMOGLOBIN AND RED BLOOD CELLS AS PROGNOSTIC INDICATOR FOR ORAL CANCER

Renata Freitas Araujo Calumby, André Leonardo de Castro Costa, Lucianna Stutz Souza Carneiro de Campos, Gessualdo Seixas Oliveira Junior, Vitor Silva de Oliveira, Herval Bruno Moreira dos Santos Filho, Geovane de Jesus Santos, Laiane da Cruz Pena, Camila da Silva Souza, Lucas Gomes Silva, Marcus Antônio de Mello Borba, Iguaracyra Araújo, Rodrigo Tripodi Calumby, Sılvia Lima Costa, Deise Souza Vilas-Bôas

Introduction: Oral Squamous Cell Carcinoma (OSCC) represents the major oral cavity tumor and presents high aggressiveness and metastasis. Particularly in Brazil, OSCC is the fifth most common cancer in males. Therefore, there is a great demand for effective prognostics tools. Hemoglobin (HB) and red blood cell count (RBC) have been suggested as a new tool in laboratorial investigations in the context of cancer. **Objectives:** This work aimed to assess prognostic value of red blood cell markers for OSCC patients. **Methods:** A total of 433 OSCC patients treated between 2008 and 2017 at Department of Head and Neck Surgery of Aristides Maltez Hospital (HAM, Salvador, Bahia) were enrolled and evaluated retrospectively. Hemoglobin (HB), red blood cell count (RBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (CMCH) and red cell distribution width (RDW) were assessed. Overall survival (OS), disease-specific survival (DSS), locoregional-free survival (LRFS) and distant recurrence-free survival (DRFS) were analyzed using Kaplan-Meier method and log-rank test. The prognostic value of red blood cell parameters was assessed by univariate and multivariate Cox regression analysis. **Results and Conclusions**: Males represented 68.8% of the sample. Most patients presented IVA (35.9%) or II (19.6%) TNM staging at diagnosis. During an average longitudinal follow-up period of 30 months, locoregional recurrence occurred in 24.5% (n = 106) of patients as well as metastasis in 13.9% (n = 60) and death from cancer in 49% (n = 212). Both low levels of HB or RBC were significantly correlated with Body Mass Index (BMI), nutritional assessment, tumor size, lymph node metastasis and advanced TNM staging ($p < 0.05$). Multivariate analysis showed low levels of HB (<13.2) or RBC (<4.5) as independent prognostic factor for OS and DSS. Low pretreatment HB and RBC levels may be considered as potential prognostic biomarkers for poorclinical outcomes and survival in OSCC. These results are part of a study that includes the assessment of pre- therapeutic immunological and hematological factors in relation to oral cancer prognosis. **Keywords:** oral cancer, prognosis, biomarkers, hemoglobin, red blood cell. **Support:** CAPES.

ASSOCIATION BETWEEN GENETIC POLYMORPHISMS IN THE IL1B AND IL6 GENES AND PERIODONTITIS IN A BRAZILIAN POPULATION

Rildo Batista Freire, Marcia Otto Barrientos, Soraya Castro Trindade, Isaac Suzart Gomes-Filho, Álvaro A. S. Cruz, Ryan dos Santos Costa, Tatiane de Oliveira Teixeira Muniz Carletto; Camila A. Figueiredo

Introduction: Periodontal disease is a public health problem both frequent and serious, found in all countries and in the various social strata, and its severity is directly related to the loss of dental elements, and consequent aesthetic sequelae, functional sequelae, nutritional sequelae, phonetic sequelae among others. Periodontitis elicits an exacerbated immune response, triggering the most severe form of the disease, evidenced by the loss of bone tissue. Existing available therapies can control the disease but none of them can achieve the cure, thus, the importance of studies that clarify its etiology. The genetic role in the development of this disease has been studied, however, new studies are needed to establish and elucidate the genetic profile of patients and its relationship to the development and progression of periodontal disease. **Objective:** To establish the association between genetic polymorphism in IL-1B, IL-6 and IL-10 genes with the development of periodontal disease. Material and methods: Our population comprises 506 individuals, divided according to the presence (n = 117) or absence (n = 389) of periodontal disease, all participants of the Programa de Controle da Asma e Rinite Alérgica da Bahia (ProAR). Genotyping and statistical analysis were performed using the MyltiEthnic AMR / AFR-8 infinium ilumina kit and PLINK 1.9 software, respectively. Logistic regression will be done in 3 different genetic models additive, dominant and recessive adjusted age, presence of obesity, mouth breathing, flossing, asthma and ancestry, considering Hardy-Weinberg equilibrium deviation (HWE 0.01). **Results:** One polymorphism in IL-1 beta gene, rs3136557 (allele X) was negatively associated with periodontitis using both additive model (OR= 0.48; 95%CI= 0.24-0.94) and recessive model (OR= 0.48; 95%CI=0.24-0.97). In IL-6 gene, rs2069841 (allele X) was positively associated with the disease in both additive model (OR= 6.61; 95%CI= 1.05-6.50) and recessive model (OR= 6.61; 95%CI= 1.05-6.50). **Conclusions:** Significant associations were found between polymorphisms within interleukins IL-1 beta and IL-6 genes with the development and progression of periodontal disease in a population of the city of Salvador. **Keywords:** Polymorphism; periodontal disease; Interleukins

ASSOCIATION BETWEEN TYPE 1 INTERFERON EXPRESSION AND RECEPTORS (INFAR1 AND INFAR2), INTERLEUKIN 17-A, ENDOGENOUS RETROVIRUS (HERV-K AND HERV-W) IN NASAL MUCOSA AND COVID-19 GRAVITY

Taiane Gondim, T.; Silva, N. N.; Reis-Góes, F.S; Figueiredo, R. G.; Evangelista, G. A. O. Meyer, R.J., Fortuna, V.; Trindade, S.C

Introduction: COVID-19 is an acute respiratory disease caused by the new SARS-CoV-2 coronavirus. In approximately 80% of cases, its course occurs withmild and moderate symptoms, but about 19% of those affected by the disease develop its severe form. The progression of COVID-19 has been associated withhypoxia, unregulated systemic inflammation and coagulopathies, however the risk factors for its evolution to the severe form are still not fully understood. Someevidence points to factors involved in the virus-host interaction, such as the impaired signaling of type I IFN – the main innate line of defense for mounting aneffective antiviral immune response – associated with an unregulated expressionof the cytokine IL-17A. In addition, human endogenous retroviruses (HERVs), remnants of ancestral viral genomic insertions, appear to be reactivated in response to infectious agents such as SARS-CoV-2, modulating the innate immune response and leading to various immunopathological effects, however role in the worsening of COVID-19 are still incipient. **Objective:** To evaluate the expression of IFN-α genes and their receptors INFAR1 and INFAR2, IL-17A, as well as HERV-K and HERV-W in nasal mucosa cell samples from individuals diagnosed with mild and severe forms of COVID-19. **Methods:** In the present case-control study, individuals over 18 years old with a diagnosis of COVID-19 by RT-PCR were divided into two groups, according to the symptoms of the disease: mild group (n=59), composed of individuals with symptoms from mild tomoderate, and severe group (n=59), composed of individuals hospitalized in tworeference hospitals. **Preliminary Results:** In the characterization of the investigation groups, some covariates were associated with the severe form of the disease, such as age ≥ 65 years (OR: 7,04; IC: 2,61-18,97; p<0.001), hypertension (OR: 2,57; IC: 1,1-5,87; p=0,023), diabetes (OR: 16,26; IC: 4,56- 57,95; p<0,001), and smoking (OR: 20,22; IC: 4,98-82,14; p<0,001). The mRNA extraction and cDNA library construction were performed and gene expression isunder

analysis by qRT-PCR. **Final Considerations:** Preliminary data indicate that the severe form of COVID-19 affects people over 65 years old, with hypertension, diabetes and smoking history. Knowledge about the immunologicaland inflammatory markers underlying these risk factors is necessary not only to elucidate the immunopathogenic mechanisms of the disease, but also to help determine the prognosis and propose new treatment approaches for severe forms of COVID-19. **Keywords**: COVID-19. Cytokines. Inflammation. Nasal mucosa. **Support:** FAPESB, CNPq and PIBIC-UFBA.

IMMUNOLOGICAL RESPONSE BOROILERS CHICKENS FED WITH DIET SUPPLEMENTED WITH ZINC

Tatiane Almeida Viana Lopes; Jerônimo Ávito De Brito; Alexandre Moraes Pinheiro

Introduction: Zinc (Zn^{2+}) is a micromineral that is a cofactor of a large number of enzymes, which is involved in several metabolic processes and is crucial for the proper development of the entire immune system. The immune response of birds is similar to that of mammals, in these animals this response can be influenced by the composition of the diet. **Objectives:** The aim of this work wasto evaluate the effect of zinc supplementation in broiler chickens on the immune response. **Material and Methods:** 832 one-day-old male chicks were used in a completely randomized design with 4 treatments: (1-Control (basal diet without zinc supplementation); 2- ZnO-100 (basal diet + zinc oxide, 100mg / kg Zn); 3 – Gl-Zn25 (basal diet + zinc glycinate, 25mg/kg Zn) and 4-Gl-Zn100 (basal diet + zinc glycinate 100mg/kg Zn) in 8 repetitions with 26 birds per The cellular immune response was evaluated through cell proliferation and nitric oxide production in peripheral blood mononuclear cell cultures, in addition to thecutaneous basophil response using the phytohemagglutinin-P test. The humoralresponse was performed with the evaluation of antibody titers against sheep redblood cells. In addition, the ratio of heterophylls/lymphocytes was evaluated. **Results and discussion:** Supplementation with the organic source of zinc (25mg/kg) stimulated cell proliferation ($p<0.05$) and the animals that received this treatment. o presented greater weight gain considering the entire period of the experiment ($p<0.05$). There was a higher production of nitric oxide, at 6.77 pg/µg of protein, with the level of inorganic zinc (ZnO) in the supplementation of 100mg/kg ($p<0.05$). **Conclusions**: The results presented suggest that supplementation of broilers diet with zinc may be beneficial to the immune system of broilers.Keywords: immune system, broilers, zinc.**Support**: CAPES; UFRB.

AGATISFLAVONA MODULA A RESPOSTA GLIAL EM UM MODELO EX VIVO DE TRAUMA DE CÉREBRO

Verônica Moreira de Sousa, Áurea Maria Alves Nunes Almeida, Fillipe Mendes De Araújo Rafael Short Ferreira, Cleonice Creusa dos Santos, Silvia Lima Costa

Traumatic Brain Injury (TBI) is a complex and multifactorial pathology, being a major cause of death and disability for humans. Immediately after TBI, astrocytes and microglia react with complex morphological and functional changes known as reactive gliosis and forms, in the area immediately adjacent to the lesion, the glial scar, the major barrier to neuronal regeneration in the central nervous system. The flavonoid agathisflavone (bis-apigenin) has been shown to have neurogenic, neuroprotective and anti-inflammatory effects, demonstrated in in vitro models of glutamate-induced toxicity, neuroinflammation, demyelination and trauma. In a previous study, agathisflavone modulated astrogliosis and improved neurite outgrowth in a in vitro scratch wound model of TBI, effects associated with modulation of increased expression of the neurotrophic factors NGF and GDNF, which are associated with the neuroprotective profile of glial cells. However, the mechanisms mediating agathisflavone action in TBI models are still poorly understood. The present study investigated the effect of agathisflavone in neuronal integrity and in the modulation of astrocytes and microglia response in an ex vivo model. For this, microdissections from the encephalon of Wistar rats (P6-8), were prepared and subjected to mechanical injury prior to treatment with agathisflavone (5µM), and in the daily changes of the culture medium by 3 days or maintained in control conditions (DMSO0.005%). For cell phenotype and morphology analyses, the cells were immunolabeled for β-III-tubulin (neurons), GFAP (astrocytes), and Iba-1 (microglia). In the lesion area of the untreated groups, decreased immunostaining of β-III tubulin was observed, as well as gliosis

in the extension of the edge of the lesion, evidenced by the increase increase in the proportion of microglia, increase of GFAP expression, and formation of the typical TBI glial scar. On the other hand, in the injured tissue treated with agathisflavone the expression of GFAP and the extension of the glial scar were reduced, associated with attenuation of microglia response, and with the increase of neurons in the area and edge of the lesion. These results indicate that the flavonoid was able to modulate gliosis and increase the population of neuronal cells and the migration of neurons to the region of brain injury putting in perspective its use in complementary therapies for TBI. **Keywords:** Traumatic brain injury, Agathisflavone, Astrogliosis, Microglia **Financing source:** CAPES, FAPESB and CNPq.

SEPTEMBER 6 – 9 , 2021 - VIRTUAL

VI INTERNATIONAL SYMPOSIUM OF NEUROCHEMISTRY AND PATHOPHYSIOLOGY OF THE GLIAL CELL

Laboratory of Neurochemistry and Cellular Biology (LabNq)
Federal University of Bahia (UFBA) - Brazil

September 6 – 9, 2021

ORGANIZATION:

Laboratory Of Neurochemistry and Cellular Biology(LabNq)
Federal University Of Bahia (UFBA) – Brazil

GENERAL COORDINATOR:

Silvia Lima Costa

SCIENTIFIC COMMISSION:

Balbino Lino dos Santos
Clarissa de Sampaio Schitine
Juciele Valeria Ribeira de Oliveira
Maria de Fátima Dias Costa
Suzana Braga de Souza
Victor Diogenes Amaral da Silva.

SESSION COORDINATORS:

Balbino Lino dos Santos
Clarissa de Sampaio Schitine
Maria de Fatima Dias Costa
Juciele Valeria Ribeira de Oliveira
Ravena Pereira do Nascimento
Silvia Lima Costa
Suzana Braga de Souza
Victor Diogenes Amaral da Silva

STUDENTS ORGANIZING TEAM:

Carol Parente
Catarina de Jesus
Irlã Lima
Lucas Oliveira
Lucia Santana
Monique Santana
Rafael Short
Rodrigo Carreira
Vanessa Freitas
Vinicius Serafim

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Endereço: Instituto de Ciência da Saúde (ICS) – Universidade Federal da Bahia (UFBA). Av. Reitor Miguel Calmon, s/n.º, Vale do Canela. CEP: 40.110-100 Salvador Bahia Brasil. Fone: (0xx71) 3283 – 8959. Fax: (0xx71) 3283 – 8894. E-mail: cimedbio@ufba.br
Site: http: //www.portalseer.ufba.br/index.php/cmbio/
Revisão dos textos em Português: Prof Roberto Paulo Correia de Araújo – Universidade Federal da Bahia – UFBA, Brasil; Marcelo Andrade Silva Santos – UFBA, Brasil; Keite Birne de Lira – Brasil
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SUMÁRIO

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PRESENTATION

The 6th International Symposium on Neurochemistry and Pathophysiology of the Glial Cell took place totally virtually from the 6th to the 9th September 2021 through the Zoom Platform. The event feature besides local researchers the participation of renowned speakers from Brazil, the Americas and invited researchers from Europe and Oceania, which addressed the various topics that involve research in Neurochemistry, Pathophysiology, Neuro and Immunopharmacology and all its related. During the event it was presented and discussed advances in the understanding of aspects of neurochemistry, immunology, physiology, and pathophysiology of diseases that affect the nervous system and about the understanding of molecular targets for drug discovery, organized in conferences, scientific session also composed by young researchers, as well as virtual poster session. Around 300 participants attended the meeting, between undergraduate students and graduate students, as well as researchers and professionals, which will bring the possibility of interaction of the local academic and scientific community with renowned researchers, encouraging scientific and technological exchanges.

PROGRAM

September 6th

MINICURSO PRÉ-SIMPÓSIO

Bases of the knowledge of Research in Neurochemistry

School of Advanced Studies in Neurochemistry (EAENq)

09:00 10:30 Balbino Lino dos Santos and (LabNq-ICS/UFBA) – Morphofunctional aspects of Central Nervous System (CNS) cells.

10:30 12:00- Silvia Lima Costa LabNq-ICS/UFBA) – In vitro study models of CNS cells under physiological and pathological conditions.

13:00-15:00 h – Victor Diógenes Amaral da Silva (LabNq-ICS/ UFBA) – In vivo Study Models of CNS Pathologies. [Modelos de Estudo in vivo de Patologias do SNC.] Prof. Victor Diogenes Amaral da Silva

15:00-17:00 – Maria Trinidad Herrero and Lorena Cuenca-Bermejo (Universidade de Murcia, ES) – Octodon as a model of both cerebraland systemic aging. Maria Trinidad Herrero and Lorena Cuenca-Bermejo.

September 7th

09:30 Symposium Opening – Silvia Lima Costa

10:00-11:00 Maria Trinidad Herrero (University of Murcia, ES). – Aspects of neuroinflammation associated with Parkinson's disease.

11:00-12:00 Luis Barbeito (Instituto Pasteur Montevideo, UR) Cellular senescence in neurodegenerative disease

13:00-15:30 h Round Section

Arthur Butt (University of Portsmouth- UK) – The yin and yang of neurotransmitter signalling in CNS white matter

Andrea Rivera (University of Padua -IT, University of Portsmouth- UK) – Decline of oligodendrogenesis and myelination in the ageing white matter.

Patrick Kuery (Heinrich-Heine-University of Dusseldorf, GE) – Of Endogenous Retroviruses and Glial Cells and their Roles in Neurodegeneration and Myelin Repair

Cleide Souza (University of Sheffield, UK) Decodificando vulnerabilidade e resiliência neuronal na Esclerose Lateral Amiotrófica (ELA). Decoding Neuronal Vulnerability and Resilience in Amyotrophic Lateral Sclerosis (ALS)

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September 8th

09:00-10:00- Video-posters Section I

10:00-11:00- Gilles Gullemin (Macquarie University, AUS) -Glioblastomas, the kynurenine pathway and resistance to chemotherapy

11:00-12:00 Henning Ulrich (USP)

Purinergic signaling in Parkinson's and Huntington's disease

13:00-15:30 h – Round Section

Sassan Hafisi (University of Portsmouth- UK) – Regulation of neuroinflammation by Gas6/TAM signalling

Bruno Solano (IDOR, IPGM-Fiocruz-BA) – Stem cells to model and treat neurodevelopmental disorders

Gustavo Dubois (ICB/UFRJ) Metabolic and genetic contributions for human glioma development

Silvio do Desterro Cunha (IQ/UFBA) Pseudo natural products as cytotoxic scaffolds to glia cell

Pseudo produtos naturais como protótipos citotóxicos para célula glial

September 9th

09:00-10:00- Sess Video-posters Section II

10:00 – 12:00 – Round Section

Emiliano Trias (Instituto Pasteur, UR) – The pathogenic role of c-Kit+ mast cells in the spinal motor neuron-vascular niche in ALS

Fillipe Mendes (LabNq/UFBA, INIFACS) – Flavonoid Rutin regulates glial cells response and protects dopaminergic neurons against aminochrome neurotoxicity**.**

Balbino Lino dos Santos (LabNq/UFBA, UNIVASF) – Phytoestrogen agathisflavone modifies microglial activation state associate with neuroprotection

13:00-15:30 h Round Section

George Barreto (University of Limerick, IR)- Repurposing of tibolone in neurometabolic diseases.

Gustavo José da Silva Pereira (UNIFESP) – Cannabidiol induces autophagy in neuronal cells: possible impact on neurodegenerative diseases

Ricardo Reis (UFRJ) The endocannabinoid system, diet based on polyunsaturated fatty acids (PUFAS) and quality of life

15:30 h Closure

ABSTRACTS OF CONFERENCES

CELLULAR SENESCENCE IN NEURODEGENERATIVE DISEASE

Luis Barbeito and Emiliano Trias

Institut Pasteur de Montevideo, Uruguay

Age is a recognized risk factor for amyotrophic lateral sclerosis (ALS), a paralytic disease characterized by progressive loss of motor neurons and neuroinflammation. A hallmark of aging is the accumulation of senescent cells. Yet, the pathogenic role of cellular senescence in ALS remains poorly understood. In rats bearing the ALS-linked SOD1G93A mutation, microgliosis contribute to motor neuron death, and its pharmacologic downregulation results in increased survival. Here, we have explored whether gliosis and motor neuron loss were associated with cellular senescence in the spinal cord during paralysis progression. In the lumbar spinal cord of symptomatic SOD1G93A rats, numerous cells displayed nuclear p16INK4a as well as loss of nuclear Lamin B1 expression, two recognized senescence-associated markers. The number of p16INK4a-positive nuclei increased by four-fold while Lamin B1-negative nuclei increased by 1,2-fold, respect to non-transgenic or asymptomatic transgenic rats. p16INK4a-positive nuclei and Lamin B1-negative nuclei were typically localized in a subset of hypertrophic Iba1-positive microglia, occasionally exhibiting nuclear giant multinucleated cell aggregates and abnormal nuclear morphology. Next, we analyzed senescence markers in cell cultures of microglia obtained from the spinal cord of symptomatic SOD1G93A rats. Although microglia actively proliferated in cultures, a subset of them developed senescence markers after few days in vitro and subsequent passages. Senescent SOD1G93A microglia in culture conditions were characterized by large and flat morphology, senescence-associated beta-Galactosidase (SA-β-Gal) activity as well as positive labeling for p16INK4a, p53, matrix metalloproteinase-1 (MMP-1) and nitrotyrosine, suggesting a senescent-associated secretory phenotype (SASP). Remarkably, in the degenerating lumbar spinal cord other cell types, including ChAT-positive motor neurons and GFAP-expressing astrocytes, also displayed nuclear p16INK4a staining. These results suggest that cellular senescence is closely associated with inflammation and motor neuron loss occurring after paralysis onset in SOD1G93A rats. The emergence of senescent cells could mediate key pathogenic mechanisms in ALS.

Keywords: Senescence, glial cells, ALS

Support: Institut Pasteur de Montevideo

REPURPOSING OF TIBOLONE IN NEUROMETABOLIC DISEASES

George E. Barreto

Department of Biological Sciences, University of Limerick, Limerick, Ireland

Neurodegenerative diseases or acute brain trauma represent a high morbidity in the world population. Most of these injuries severely alter the correct functioning of the Central Nervous System (CNS), which implies the modification of the neuronal and glial microenvironment in response to the insult. Furthermore, the progression of these diseases is the consequence of exacerbated inflammatory processes that lead to a continuous and systematic deterioration of brain tissue. Recent studies show that accumulation of lipids within the brain plays a key role in the post-injury period, which is characterized by chronic activation of glial cells and mitochondrial dysfunction with a significant impact over neuronal homeostasis. The search for neuroprotective strategies that can modulate the neuroinflammatory response and reduce neuronal loss by regulating activated glia is of clinical interest. One FDA-approved drug with anti-inflammatory, anti-apoptotic and antioxidant properties is tibolone, a drug in use by postmenopausal women that has been object of study by our group in the last few years. This is a prodrug, meaning that it produces no actions over cells, but once metabolized will give rise to metabolites with the ability to selectively interact with estrogen, androgen or progesterone receptors in a tissue-specific manner. Interestingly, activation of these receptors in various brain diseases is neuroprotective and has been well explored. We previously reported that by regulating both NF-κB signaling and stimulating the expression of neuroglobin tibolone decreased oxidative stress and inflammation in both astrocytes and microglia exposed to lipotoxic damage. Many of tibolone's protective benefits are in part mediated by estrogen receptor beta, suggesting the importance of this receptor in facilitating the estrogenic action of tibolone and

its associated genomic effects. Given the broad pharmacological effects of tibolone by acting over various receptors, this drug may be considered suitable for repurposing in brain diseases, especially in those related with dysfunctional lipid metabolism.

Keywords: Tibolone; Brain diseases; neuroprotection.

Support: Science Foundation Ireland (SFI), Irish Research Council (IRC), ULCaN (UL) – Health Research Institute.

CANNABIDIOL INDUCES AUTOPHAGY VIA ERK1/2 ACTIVATION IN NEURAL CELLS

Talita A M Vrechi [1], Anderson H F F Leão [1], Ingrid B M Morais [1], Vanessa C Abílio [1], Antonio W Zuardi [2 3], Jaime Eduardo C Hallak [2 3], José Alexandre Crippa [2 3], Claudia Bincoletto [1], Rodrigo P Ureshino [4 5], Soraya S Smaili [1], Gustavo J S Pereira [1]

[1] Department of Pharmacology, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP, Brazil; [2] National Institute for Translational Medicine (INCT-TM), National Council for Scientific and Technological Development (CNPq/CAPES/FAPESP), Ribeirão Preto, Brazil; [3] Department of Neuroscience and Behavior, Ribeirão Preto Medical School, Universidade de São Paulo, USP, Ribeirão Preto, Brazil; [4] Department of Biological Sciences, Diadema Campus, Universidade Federal de São Paulo, Diadema, SP, Brazil;[5] Laboratory of Molecular and Translational Endocrinology, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP, Brazil; [6] Department of Pharmacology, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP, Brazil.

Autophagy is a lysosomal catabolic process essential to cell homeostasis and is related to the neuroprotection of the central nervous system. Cannabidiol (CBD) is a non-psychotropic phytocannabinoid present in Cannabis sativa. Many therapeutic actions have been linked to this compound, including autophagy activation. However, the precise underlying molecular mechanisms remain unclear, and the downstream functional significance of these actions has yet to be determined. Here, we investigated CBD-evoked effects on autophagy in human neuroblastoma SH-SY5Y and murine astrocyte cell lines. We found that CBD-induced autophagy was substantially reduced in the presence of CB1, CB2 and TRPV1 receptor antagonists, AM 251, AM 630 and capsazepine, respectively. This result strongly indicates that the activation of these receptors mediates the autophagic flux. Additionally, we demonstrated that CBD activates autophagy through ERK1/2 activation and AKT suppression. Interestingly, CBD-mediated autophagy activation is dependent on the autophagy initiator ULK1, but mTORC1 independent. Thus, it is plausible that a non-canonical pathway is involved. Our findings collectively provide evidence that CBD stimulates autophagy signal transduction via crosstalk between the ERK1/2 and AKT kinases, which represent putative regulators of cell proliferation and survival. Furthermore, our study sheds light on potential therapeutic cannabinoid targets that could be developed for treating neurodegenerative disorders.

Keywords: autophagy, cannabidiol, neuroprotection

Support: CAPES, CNPq, FAPESP.

PURINERGIC SIGNALING IN PARKINSON'S AND HUNTINGTON'S DISEASE

Henning Ulrich

Department of Biochemistry, Institute of Chemistry, University of São Paulo, São Paulo / SP, Brazil

Purinergic receptors have been shown to be important for development and tissue regeneration. Here, we have explored the participation of purinergic receptors in brain diseases, such as Parkinson´s and Huntington´s disease, using in vitro and in vivo models. Purinergic P2Y2, P2Y6 and P2X7 receptors have been previously studied in our laboratory regarding their roles in neural proliferation differentiation of stem cell models. Here, we link these receptors to their involvement in neurodegeneration and provide novel promising targets for therapeutic approaches. Parkinson's disease is a neurodegenerative disorder characterized by dopaminergic neuron death and decreased dopamine availability in the substantia nigra and striatum. Unilateral dopaminergic neuron degeneration was induced in the rat model by 6OH-dopamine (6OHDA) injection. Lesion establishment was confirmed after one week by rotational tests for confirming

hemiparkinsonian behavior and by immunohistochemical analysis. P2Y6 and P2X7 receptor blockade was investigated for preventing or reversing hemiparkinsonian behavior and dopaminergic neuron deficits in this animal model. P2X7 receptor antagonism with Brilliant Blue G reestablished dopaminergic ramifications in the striatum of rats injured with 6-OHDA following a period from 7 days on. Further, P2Y6 receptor blockade prevented dopaminergic neuron death in the substantia nigra of 6-OHDA-injured rats. Moreover, both treatments were accompanied by a reduction of microglial activation. Altogether, antagonism of P2X7 and P2Y6 receptors mediated neuroregenerative and neuroprotective effects, respectively, possibly mediated through modulation of neuroinflammatory responses. Huntington's disease (HD), an autosomal dominant inherited disease caused by at least 35 repetitions of the N-terminal CAG trinucleotide (glutamine) in the Huntington's gene, results in the loss of basal ganglia GABAergic neurons leading to motor, mood and cognition impairment and uncontrolled movements. HD was modeled in vitro using CRISPR-Cas9 modified embryonic stem and HD patient-iPS cells induced to neuronal differentiation. P2Y2 receptor activation promoted cell fate commitment to GABAergic neurons, providing a pharmacological target for therapeutic intervention. In summary, the here shown results of in vitro and in vivo studies point at the importance of purinergic receptors in neurodegeneration and open avenues for novel therapeutic applications involving the purinergic system. Further studies with psychiatric diseases, such as Alzheimer's and bipolar disease, are underway.

Keywords: Purinergic signaling; Parkinson's disease; Huntington's disease

Support: Grants and fellowships awarded by FAPESP, CNPq and CAPES (Brazil).

THE ENDOCANNABINOID SYSTEM, DIET BASED ON POLYUNSATURATED FATTY ACIDS (PUFAS) AND QUALITY OF LIFE

Ricardo A de Melo Reis[1], Alinny R Isaac[1], Hércules R Freitas[1], Luzia S Sampaio[1], Clarissa S Schitine[2], Regina CC Kubrusly[3], Belmira LS Andrade-da-Costa

[1]Lab de Neuroquímica, Instituto de Biofísica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, [2] Laboratório de Neuroquímica e Biologia Celular, Instituto de Ciências da Saúde, Universidade Federal da Bahia, [3] Lab de Neurofarmacologia, Instituto Biomedico, Universidade Federal Fluminense, [4]Laboratory of Neurophysiology, Department of Physiology and Pharmacology, Federal University of Pernambuco, Recife, Brasil

The endocannabinoid system (ECS) is an important brain modulatory network. Endocannabinoids (eCBs) mediate significant effects in the fine-tune adjustment of body homeostasis, involved in obesity, depression and drug addiction. We have shown that the ECS is involved in neurogenesis and oligodendrogenesis in neurogenic niches as in the subventricular zone area (SVZ). In the retina, it's a major player highly expressed early from embryonic stage, decreasing its levels throughout development; cannabinoid receptors (CBR) function as regulators of retinal neuro-glial circuits signaling during synapse formation; On the other hand, omega-3 (n-3) polyunsaturated fatty acids (PUFA) and the ECS modulate several functions through neurodevelopment including synaptic plasticity mechanisms. The effects of maternal n-3PUFA supplementation (n-3Sup) or deficiency (n – 3Def) on ECS and synaptic markers in postnatal offspring will be discussed. Female rats were fed with a control, n – 3Def, or n-3Sup diet from 15 days before mating and during pregnancy. The cerebral cortex and hippocampus of mothers and postnatal 1-2 days offspring were analyzed. In the mothers, n – 3Def reduced CB1R protein levels in the cortex and increased CB2R in both cortex and hippocampus. In neonates, a maternal n – 3Def reduced the hippocampal CB1R amount while it increased CB2R. Maternal n-3Sup also increased PKA phosphorylation in the cortex and ERK phosphorylation in the hippocampus. The findings show that variations in maternal dietary omega-3 PUFA levels may impact differently on the ECS and molecular markers in the cerebral cortex and hippocampus of the progeny. To live a better life implies in a vigilant ECS, through healthy diet selection, weekly exercises and meditation therapy, all of which regulate eCBs levels, surrounded by a constructive social network. Cognitive challenges and emotional intelligence might strengthen the ECS, which is built on a variety of synapses that modify human behavior.

Keywords: cannabinoid, omega-3, diet

Support: Faperj, CNPq, INNT

THE PATHOGENIC ROLE OF C-KIT+ MAST CELLS IN THE SPINAL MOTOR NEURON-VASCULAR NICHE IN ALS

Mariángeles Kovacs, Luis Barbeito, Emiliano Trias

Institut Pasteur de Montevideo

Degeneration of motor neurons, glial cell reactivity, and vascular alterations in the CNS are important neuropathological features of amyotrophic lateral sclerosis (ALS). Immune cells trafficking from the blood also infiltrate the affected CNS parenchyma and contribute to neuroinflammation. Mast cells (MCs) are hematopoietic-derived immune cells whose precursors differentiate upon migration into tissues. Upon activation, MCs undergo degranulation with the ability to increase vascular permeability, orchestrate neuroinflammation and modulate the neuroimmune response. However, the prevalence, pathological significance, and pharmacology of MCs in the CNS of ALS patients remain largely unknown. In autopsy ALS spinal cords, we identified for the first time that MCs express c-Kit together with chymase, tryptase, and Cox-2 and display granular or degranulating morphology, as compared with scarce MCs in control cords. In ALS, MCs were mainly found in the niche between spinal motor neuron somas and nearby microvascular elements, and they displayed remarkable pathological abnormalities. Similarly, MCs accumulated in the motor neuron-vascular niche of ALS murine models, in the vicinity of astrocytes and motor neurons expressing the c-Kit ligand stem cell factor (SCF), suggesting an SCF/c-Kit-dependent mechanism of MC differentiation from precursors. Mechanistically, we provide evidence that fully differentiated MCs in cell cultures can be generated from the murine ALS spinal cord tissue, further supporting the presence of c-Kit+ MC precursors. Moreover, intravenous administration of bone marrow-derived c-Kit+ MC precursors infiltrated the spinal cord in ALS mice but not in controls, consistent with aberrant trafficking through a defective microvasculature. Pharmacological inhibition of c-Kit with masitinib in ALS mice reduced the MC number and the influx of MC precursors from the periphery. Our results suggest a previously unknown pathogenic mechanism triggered by MCs in the ALS motor neuron-vascular niche that might be targeted pharmacologically.

Keywords: Mast cells, ALS, neuro-vascular niche

Support: Institut Pasteur de Montevideo

DECLINE OF OLIGODENDROGENESIS AND MYELINATION IN THE AGEING WHITE MATTER.

Andrea D. Rivera[1-2], Veronica Macchi[1], Andrea Porzionato[1], Raffaele De Caro[1] and Arthur M. Butt[2]

[1]Department of Neuroscience, Institute of Human Anatomy, University of Padua, Padua, Italy; [2]School of Pharmacy and Biomedical Science, University of Portsmouth, Portsmouth, UK

Oligodendrocytes (OLs) are specialised glial cells that myelinate axons in the central nervous system (CNS). Myelinated axons are bundled together into white matter (WM) tracts that are essential for rapid, integrated neuronal communication and cognitive function. A population of adult oligodendrocyte progenitor cells (OPCs) is responsible for the life-long generation of OLs, which is essential to replace myelin lost in pathology. Recently, we have demonstrated that there is a marked loss of OPCs in the aging murine bran, which is associated with the loss of WM and cognitive decline. To examine the underlying causes of age-related myelin loss in humans, we performed an in silico transcriptomic analysis of Intralobular WM of human samples from the UK Brain Expression Consortium (UKBEC), and samples were assigned to one of two age groups: young (18-31, n=20) or old (71-96, n=20). Differential Expression (DE) analysis identified a marked decline in oligodendroglial genes, including the OPC gene PDGFRA and the myelin genes MBP and MOBP, supporting our recent findings in mice. Functional protein-protein network and Gene Ontology (GO) analyses highlighted that the biological pathways most disrupted in aging human WM were involved in Neurogenesis, Cognition, and CNS Development. Moreover, Pathway Analysis identified age-related perturbation of G-Protein Receptor Signalling and MAPK Signaling pathways, which are known to be key regulators of oligodendrogenesis and myelination. Next, we used a pharmacogenomic and functional protein-chemical network analysis approach to discover potential therapies for rejuvenating OPCs in the ageing human brain, and the result show that the PI3K/AKT/MTOR signalling pathway was one of the most important therapeutic targets to stimulate oligodendrogenesis in the aging human WM. To test this, we used the WM model of mouse optic nerve organotypic culture and demonstrate the PI3K/AKT modulator LY294002 profoundly promotes oligodendrogenesis. These studies determine key changes in OLs that underlie the

decline in myelination in the ageing brain. Furthermore, we identify drugs that target pro-oligodendroglial signalling pathways as potential new therapies for promoting life-long generation of OLs and maintaining cognitive function.

Keywords: Oligodendroglia, GPR17, PI3K/AKT

Support: Sponsored by BBSRC, Marie-Sklodowska Curie Action @ UNIPD

ABSTRACTS OF VIDEO-POSTERS

ANALYSIS OF THE ACTION OF RUTIN IN AN AMINOCHROME INDUCED MODEL

Alana Alves Farias[1]; Deivison Silva Argolo[1]; Matheus Nolasco[2]; Ana Carla dos Santos Costa[1]; Alexsandro Branco[2]; Silvia Lima Costa[1]; Victor Diógenes Amaral da Silva[1]* and Maria de Fátima Dias Costa[1]*

*[1] Laboratory of Neurochemistry and Cell Biology, Department of Biochemistry and Biophysics, Institute of Health Sciences, Federal University of Bahia. [2] Phytochemistry Laboratory Health Department, State University of Feira de Santana – UEFS, Feira de Santana, BA, 44036-900, Brazil. *Corresponding authors: Instituto de Ciências da Saúde Av. Reitor Miguel Calmon s/nº Vale do Canela, Salvador-Bahia, 40110-902, Brazil. Tel.: 55 71 3283 8919; fax: +55 71 3283 8927. E-mail address: vdsilva@ufba.br (VDAS); costasl@ufba.br (MFDC).*

Background: Parkinson's disease (PD) is characterized by neurodegeneration with progressive impairment of dopaminergic neurons. Nowadays it is well established that brain inflammatory processes play a fundamental role in its etiopathogenesis. PD has been studied through the kynurenine pathway (KP), which catabolizes tryptophan (TRP), generating neuroactive metabolites, among which quinolinic acid (QUIN) agonist of NMDA receptors and kinurenic acid (KYNA), antagonist of these receptors. Astrocytes and microglia express several KP enzymes, whose activation may favor neuroprotection or induce neurotoxicity. On the other hand, the flavonoid rutin, extracted from the plant Dimorphandra mollis, has shown antioxidant and anti-inflammatory actions in a PD model by aminochrome cell damage. **Objectives:** To analyze the morphology of glial cells and the presence of KP catabolites after aminochrome damage and rutin treatment. **Methods:** glial cells from rat brain were cultured and modulated with 25µM of aminochrome for 24 hours and then treated with 1 µM of rutin solution for 24 hours. Control and treated cultures were analyzed by immunocytochemical technique using anti GFAP antibody for immunostaining of astrocytes. The culture medium/secretome was filtered, precipitated with methanol at 4°C and analyzed by HPLC on a reverse phase column (C18) at 22°C with the solvents methanol, acetonitrile and water and eluates detected between 280-360 nm compared to standard solutions of the catabolites (QUIN, KYNA, 3-hydroxykynurenic in addition to TRP). **Results and Conclusions:** Treatment with aminochrome showed morphological changes in astrocytes, with a decrease in the cell body and lower expression of GFAP; aminochrome damage was reversed by rutin, showing a morphology and organization of the cell monolayer similar to the control group, in addition to an increase in GFAP expression. In cultures treated with aminochrome, the chromatographic analysis showed a peak compatible with the QUIN pattern, while in the aminochrome + rutin group, a chromatographic peak compatible with KYNA was detected. The results suggest that rutin was able to reverse the cell damage induced by aminochrome with a reduction in astrogliosis, in addition to favoring the production of kinurenic acid, which may controls complications of the inflammatory process.

Keywords: Parkinson's disease, neuroinflammation, kynurenines pathway, rutin, aminochrome.

Support: CNPQ

THE ROLE OF THE ABC-TRANSPORTER ABCC1 IN GLIOBLASTOMA AGGRESSIVE PHENOTYPE

Carlos Eduardo Pilotto Heming [a 1,2], Wanjiru Muriithi [c 1,2], Vivaldo Moura Neto [b 1,2]

[1] Instituto Estadual do Cérebro Paulo Niemeyer, Rio de Janeiro, 20231-092. [2] Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro. [a.] ceheming@ufrj.br, Tel +5521987101998. [b.] vivaldomouraneto@gmail.com, Tel +552122779393. [c.] cjshiru@gmail.com, Tel +5521971753061

Background: The high expression of efflux pumps of the family of ATP – Binding Cassette transporters (ABC-transporters) and in particular the multidrug resistance – associated protein 1 (MRP-1) has been linked to Glioblastoma (GB) malignancy. Although studies have concentrated on its role in multidrug resistance phenotype, recent reports in different cancers have established that MRP-1 and other ABC-transporters have additional roles in tumor biology. Dysregulation involving either upregulation or downregulation have been shown to promote tumor formation and progression. We sought to determine whether MRP-1 contributes to drug resistance and migration GB. **Materials and Methods:** Using laboratory derived and commercial GB cell lines, gene knock-out using CRISPR – cas9 was done followed by characterization of knockouts and functional assays to determine the role of MRP-1 transporter in GB aggressiveness. **Results and Conclusion:** The ABCC1 gene was successfully knocked out in T98G and GBM03 cell lines. Treatment of knock-out cell lines with vincristine showed significant response compared to controls and surprisingly, temozolomide which is not a substrate of MRP-1 also showed increased action in knock-outs. Cell migration was significantly diminished $P<0.001$ in knockout. These results show that the upregulation of MRP-1 expression in glioblastoma plays a poignant role in its aggressive phenotype by upregulating migration and increased drug resistance. This study contributes to the growing works that positions ABC-transporters as important potential targets against glioblastoma progression and in the development of personalized medicine strategies.

Keywords:

EFFECTS OF COMPOUNDS DERIVED FROM *AMBURANA CEARENSIS* ON MODULATION OF GLIAL RESPONSE DURING IN VITRO INFLAMMATORY DAMAGE

Cleonice Creusa Dos Santos[1,3], Erica Victória Misan[1,3], Áurea Maria Alves Nunes Almeida[1,3], Rafael Short[1], Luzimar Gonzaga Fernandez[2], Paulo Roberto Ribeiro[2], Victor Diógenes Amaral Da Silva[1,3], Silvia Lima Costa[1,3]

[1] Laboratory of Neurochemistry and Cellular Biology, Biochemistry and Biophysics Department, Health Sciences Institute, Federal University of Bahia, Salvador, Bahia (BA),[4]0.[11]0-90[2], Brasil. [2] Laboratory of Biochemistry, Biotechnology and Bioproducts, Health Sciences Institute, Federal University of Bahia, Salvador, BA, Brasil. [3] Postgraduate Program in Immunology, Federal University of Bahia, Salvador, Bahia (BA), [4]0.[11]0-90, Brazil

Background: Compounds from *Amburana cearensis*, an indigenous plant present in the Northeast Brazil, has been widely studied for its antioxidant activity. More recently, the neuroprotective activity of extracts obtained from iA. Seeds was demonstrated, related to modulation of astrocyte reactivity. These effects were attributed to coumarins and methyl-esters present mainly in the dichloromethane (EDAC). **Objective:** This study evaluated the effect of the a EDAC and its purified cumarin on the inflammatory profile of microglia in primary cultures of glial cells submitted to inflammatory damage. **Material and methods:** Primary cultures of glial cells from the cerebral cortex of newborn Wistar rats were performed. The cells were treated with EDAC (1 µg/mL) orits coumarin (1 µM) extracted from *A. cearensis* seeds, with or without co treatment with lipopolysaccharide from Escherichia coli (LPS,1 µg/ml). To assess microglial reactivity, immunofluorescence labeling was performed for Iba-1, a microglial marker, and CD68, an indicator of a activated inflammatory profile. **Results and discussion:** Cells exposed only to LPS showed reduced ramification compared to control. In response to the concomitant exposure to LPS and coumarin, there was an increase in microglial ramification relative to cells exposed to LPS and to the control group. Moreover, the proportion of microglia in the cultures was reduced in response to co-treatment with LPS and EDAC compared to the other groups. Cells exposed only to LPS showed increased expression of CD68 compared to control. CD68 expression was reduced in response to co-exposure to LPS and coumarin, as well as to co exposure to LPS and EDAC, similar to the control. Moreover, the proportion of microglia in the cultures was reduced These data suggest that EDAC and coumarin reduce the

LPS-induced microglial proinflammatory response. Its anti inflammatory action mechanisms should be elucidated in further studies to allow the use of coumarin and other *A. cearensis* derivatives in the treatment or amelioration of neuroinflammatory and neurodegenerative processes.

Keywords: *Amburana cearensis*, LPS, inflammation, microglia.

Support: Foundation for Research Support of the State of Bahia (FAPESB).

EFFECTOS OF NICOTINE IN GLIAL CELLS AGAINST AMINOCHROME INDUCED CYTOTOXICITY

Érica Novaes Soares[1]; Ana Carla Costa[1]; Cleonice Creusa dos Santos[1]; Maria de Fátima Dias Costa[1]; Yussef Tsabl[2]; Rodrigo Portes Ureshino[3]; Silvia Lima Costa[1]; Victor Diogenes Amaral da Silva[1]

[1] Laboratory of Neurochemistry and Cell Biology, Department of Biochemistry and Biophysics, Institute of Health Sciences, Federal University of Bahia, Salvador, Bahia, Brazil; [2] Department of Pharmacology, Howard University College of Medicine, 520 W Street NW, Washington, DC 20059, USA; [3] Department of Biological Sciences, Campus Diadema Federal University of São Paulo (UNIFESP). São Paulo, Brazil

Background: Parkinson's disease (PD) is a neurodegenerative disorder that affects brain tissue, especially midbrain dopaminergic neurons. The loss of dopaminergic neurons results in low levels of dopamine and motor symptoms such as dyskinesia, muscle stiffness, posture instability and tremors at rest, which appear after years of degenerative processes and can be preceded by non-motor symptoms such as olfactory and mood disorders. Studies have been suggested aminochrome as an endogenous neurotoxin responsible for the dopaminergic neuron degeneration in PD. On the other hand, studies have been demonstrated that nicotine protects neuronal cells against aminochrome-toxicity. However, the protective effect of nicotine in glial cells has not yet been studied. **Objective:** The aim of this study was to evaluate the protective effect of nicotine in glial cells in in vitro model of Parkinson's disease induced by aminochrome.

Methodology: Primary microglia cultures was obtained from neonatal Wistar rats (0-2 days) cortex and mixed primary cultures was obtained from Wistar rat embryos (15 – 16 days) midbrain as described in the approved protocol CEUA 127A/2017 for animal use in experimental procedure. The mixed primary cultures were treated with 25 µM aminochrome and/ or 0.01 µM or 1 µM nicotine for 48 h. Cell viability was performed by propidium iodide test and cell morphology was analyzed by Rosenfeld's stanning. The primary culture of microglia and astrocytes was treated with nicotine at concentrations of 0.0001 µM, 0.001 µM, 0.01 µM, 0.1 µM and 1 µM and aminochrome with 25 and 50 µM for 48 h. Viability was performed by MTT and phase contrast and Rosenfeld's, lysosomal acidification analyses were reallocated by acridine orange dye, analyzed propidium iodide teste, cell morphology. **Results:** It was observed that 25 µM of aminochrome induced cell death in primary cultures, in addition to 0.01 µM and 0.1 µM of nicotine preventing aminochrome-induced cell damage. It was observed in microglia and astrocytic cultures treated with 0.01 µM and 0.1 nicotine a protective effect against aminochrome-induced cytotoxicity. **Conclusion:** We concluded that nicotine is not cytotoxic at 0.01 µM or 0.1 µM in primary midbrain culture or microglial culture, moreover it protects cells neural cells against aminochrome cytotoxicity. We suggest that more studies must be performed to characterize the mechanism of nicotine action and its effect in glial cells. At the end of the analysis, we expect characterize the effect of nicotine in glial cells and mechanism involved in its protective effect against aminochrome.

Keywords: Nicotine, aminochrome, midbrain, glial cells, Parkinson's disease.

Support: FAPESB, CAPES and CNPQ.

ISOCITRATE DEHYDROGENASE MUTATIONS RESCUE LACTATE DEHYDROGENASE-DEFICIENT CELLS FROM CELL DEATH UNDER HYPOXIA

Fernanda Conceição[1], Felipe Cordeiro[1], Victor Wanderkoke[1], Luiz Henrique Geraldo[2], Luiz Gustavo Dubois[1].

[1] Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil; [2] Yale School of Medicine, Institute of Biomedical Sciences, Cell Morphogenesis Laboratory, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil.

Background Isocitrate Dehydrogenase (IDH) mutations play a significant role in glioma tumorigenesis by disrupting cellular metabolism. It is known that these mutations change the epigenetic landscape and generate cellular heterogeneity, which promotes tumor development. However, it is not yet fully understood how cells bearing mutated-IDH (mtIDH) copies are selected and favored during tumor progression in a pre-malignant context. Lactate is a metabolite generated by Lactate Dehydrogenase (LDH) from pyruvate and ensures cell survival under hypoxic conditions especially in the central nervous system. Interestingly, mtIDH gliomas lack LDH expression, which led us to hypothesize whether such mutations could confer these cells the ability to survive under hypoxic conditions even in the absence of lactate in a pre-malignant context. Therefore, we aim to demonstrate whether: (1) mtIDH gliomas lack LDH expression; (2) knock-down of LDH expression in wild-type (wtIDH) glioma cells and murine astrocytes leads to cell death under hypoxic conditions; (3) ectopic mtIDH expression in LDH-deficient cells can prevent cell death under hypoxia. **Material and Methods:** To demonstrate LDH expression in wt and mtIDH gliomas, we performed immunohistochemistry (IHC) and WB in patient biopsies. We knocked-down LDH expression in wtIDH glioma cell lines using siRNA or CRISPR. Ectopic mtIDH expression was induced by plasmid transfection in LDH-defficient cells. Cell death was measured by Trypan Blue counting and MTT assay. **Results and Conclusion:** We identified in a set of 12 patients that mtIDH gliomas lack LDH expression in contrast to wtIDH gliomas, confirmed by IHC and WB. Murine astrocytes and GBM95 cell line that had their LDH expression knocked-down through siRNA died after 24 and 48 hours under hypoxic conditions. This observation suggests that LDH expression and subsequent lactate production are essential for cell survival in hypoxia. We therefore introduced ectopic mtIDH expression into LDH-deficient cells and observed that this expression is sufficient to rescue them from cell death under hypoxic conditions. These preliminary results suggest that mtIDH rescues LDH-deficient cells from cell death under low-oxygen conditions.

Keywords: Glioma, metabolism, Lactate dehydrogenase, isocitrate dehydrogenase, hypoxia.

Support: FAPERJ

PROSPECTIVE APPROACH ON PRIMARY CULTURES OF CEREBELLUMAS STUDYMODEL OF NEUROINFLAMMATION

Santana, L. F [1,2], Passos, F.C[2], Franchi, M. S [1], Andrade, G. B, LIMA, I. S[1], Costa, S.L*[1,2] e Silva, V. D. A* [1,2]

[1] Laboratory of Neurochemistry and Cell Biology, Department of BiochemistryandBiophysics, Institute of Health Sciences, Federal University of Bahia, Salvador, Bahia,Brazil. [2] Postgraduate Program in Immunology, Institute of Health Sciences, Federal University of Bahia, Salvador, Bahia, Brazil.

Background: Neuroinflammation is a key event in the pathogenesis of several neurodegenerative diseases. To understand cellular alterations andmolecularmechanisms underlying neuroinflammation, *in vitro* experimental models havebeenemployed. Since cerebellum is a region of the central nervous systemthat containsthe largest number of neurons and glial cells, it is an excellent model to studycellularalterations associated with neuroinflammation and neurodegeneration. Most studymodels with cerebellar cells are developed using organotypic culturesystems. However, these models are expensive, time-consuming and require large numbers of animals. In this sense, the use of primary cultures appears as na interesting alternative. **Objectives:** Thus, this work aimed to address scientific articles that used primary cultures of cerebellar cells, in order to contribute to the development of protocol improvement strategies in future investigations on neroinflammation. **Methods:** A systematic exploratory scientific prospection was carriedinthedatabases electronic databases taking into consideration all publications, withtheobjective of identifying investigations using primary cultures of cerebellar cellsinthescientific literature. **Results and Discussion:** It was identified 20 articles using primary culture of cerebellar cells from rats or mice puppies. Among them, 8 articles were studies on neuroinflammation. The articles using primary cultures of cerebellarcells were published between the years 2000

to 2020. Nevertheless, these studies failed to characterize the population of oligodendrocyte precursor cells(OPC) ormature oligodendrocytes and did not make clear the yield of neurons in culture, which would be of great relevance in neurodegeneration models. **Conclusion:** Thus, this critical review contributes to building strategies for protocol improvement in future work.

Keywords: *In vitro* study model; neuroinflammation; neurodegeneration; cerebellar cells culture.

Support: FAPESB, CAPES, CNPq.

ALPHA FREQUENCY IN GURDJIEFF MEDITATION

Naíma Loureiro de S. Costa[1], Thaise Graziele L. de O. Toutain[2], José Garcia V. Miranda[3], Abrahão F. Baptista[4], Eduardo Pondé de Sena[5]

[1] Mestranda em Processos Interativos dos Órgãos e Sistemas do Instituto de Ciências da Saúde-ICS/ UFBA, Bahia, Brasil.; [2] Doutoranda em Processos Interativos dos Órgãos e Sistemas do Instituto de Ciências da Saúde-ICS/ UFBA Bahia, Brasil.; [3] Professor Titular do Departamento de Física da Terra e do Meio Ambiente, do Instituto de Física, UFBA Bahia, Brasil.; [4] Centro de Matemática, Computação e Cognição, Universidade Federal do ABC, São Paulo, Brasil. 5 Professor Associado do Departamento de Biorregulação, do Instituto de Ciências da Saúde-ICS/ UFBA Bahia, Brasil.

Background: Meditation is a practice that aims to regulate the mental state and emotions, and can induce altered states of consciousness. Among numerous meditation techniques, the work proposed by George I. Gurdjieff, includes an attempt to balance activities from the body, the mind and the feelings. Studies conducted with electroencephalography (EEG), evaluating the meditative state, demonstrated a brain pattern characterized by increased alpha and theta amplitude, as well as differences in alpha activity between meditation and relaxation. However, this is not characterized in Gurdjieff meditators, which practice beyond sitted meditations, body exercises with music, and attentional exercises during everyday life. **Objective:** Comparing the brain activity of the alpha power during the meditation and relaxation stages and evaluate the differences between the frontal, central and occipital regions in these two states, in experienced meditators from the Gurdjieff group, in Salvador-Bahia-Brazil. **Methodology:** The data collection of the brain activity from 8 volunteers was performed by EEG. The collection protocol adopted was 6 minutes of relaxation and 12 minutes of meditation. **Results:** A significant increase in alpha power was found during meditation, when compared to relaxation. The frontal and central regions showed no differences between them for alpha power, while the occipital region showed an increase in alpha power compared to the frontal and central regions. **Conclusion:** The alpha frequency behaves differently during meditation compared to relaxation, with an increase in alpha density during the meditative state in all evaluated regions, with the occipital region being the most potent.

Keywords: Quantitative EEG. Alfa Rhythm. Relaxation. Altered State of Consciousness.

Support: CAPES e FAPESB

EXTRACT FROM *AMBURANA CEARENSIS* SEEDS PROTECTS OLIGODENDROCYTES AGAINST ISCHEMIA IN HIPPOCAMPAL SLICES

Rafael Short Ferreira[1,2], Paulo Roberto Ribeiro[3], Juliana Helena Castro e Silva[1], Juliana Bender Hoppe[4], Monique Marylin Alves de Almeida[1,2], Beatriz Correia de Lima Ferreira[1], Gustavo Borges Andrade[1], Julita Maria Pereira Borges[1], Suzana Braga de Souza[1], Luzimar Gonzaga Fernandez[5], Andrea Domenico Rivera[2], Francesca Pieropan[2], José Cláudio Fonseca Moreira[4], Silvia Lima Costa[1], Arthur Morgan Butt[2]* and Victor Diogenes Amaral da Silva[1]

[1] Laboratory of Neurochemistry and Cell Biology, Department of Biochemistry and Biophysics, Institute of Health Sciences, Federal University of Bahia – UFBA, Salvador, Bahia [4]0[11]0-90[2], Brazil; [2] Institute of Biomedical and Biomolecular Sciences, School of Pharmacy and Biomedical Sciences, University of Portsmouth, St Michael's Building, White Swan Road, Portsmouth PO[1] [2]DT, United Kingdom; [3] Metabolomics Research Group, Department of Organic Chemistry, Chemistry Institute, Federal University of Bahia – UFBA, Salvador, Bahia [4]0[17]0-[115] Brazil; [4] Department of Biochemistry, Institute of Basic Health Sciences, UFRGS, Porto Alegre, Brazil; [5] Biochemistry, Biotechnology and Bioproducts Laboratory, Institute of Life Sciences, UFBA, Salvador, Brazil.

Background: The use of parts of the *Amburana cearensis* (Allemao) A.C.Sm. species by folk medicine attracted attention, especially after the description of several biological activities. In vitro neuroprotective effects have been discovered, however the understanding of how this effect acts between glial and neuron is still uncertain. **Objective:** Oligodendrocytes, the myelinating cells of the central nervous system (CNS), are highly susceptible to ischemia and their loss has devastating effects on CNS function. Astrocytes play a critical role in uptake of glutamate and disruption of this homeostatic plays an important role in the pathophysiology of brain ischemia. Studies have demonstrated protective effects of *Amburana cearensis* seeds extracts against glutamate excitotoxicity. Here, we identified coumarin as the main component of the dichloromethane extract from *A. cearensis* seeds (EDAC) and examined its potential protective effects in mouse hippocampal slices, using the oxygen-glucose deprivation (OGD) model of ischemia. **Materials and methods:** Hippocampal slices from P10-12 transgenic SOX10-EGFP and GFAP-EGFP reporter mice were used to identify oligodendrocytes and astrocytes, respectively. Slices were maintained in normal (OGN) or in OGD conditions and treated for 2h with EDAC or sterile vehicle in controls. Immunohistochemistry for glutamine synthetase (GS) and Glutamate Transporter 1 (GLT1) was used to evaluate changes in astroglial glutamate homeostasis in the CA1 region of the hippocampus. **Results:** OGD resulted in a significant loss of SOX10+ oligodendrocytes processes, that was significantly counteracted by treatment with EDAC. Hippocampus treated with EDAC in OGD presented astrocytes with altered morphology and increased expression of Glial Fibrillary Acidic Protein (GFAP), but not in GS or GLT1. **Conclusion:** These results provide the first evidence of protective effects of compounds present in *A. cearensis* seeds in oligodendrocytes following ischemic insult and indicate that modulation of astrocyte reactivity may be involved in the mechanism of protection by EDAC against ischemic injury in hippocampus.

Keywords: *Amburana cearensis*; hippocampus; oligodendrocyte; astrocyte; stroke.

Support: FAPESB, CNPq and MS Society of the UK

SYNTHESIS AND INHIBITION EVALUATION OF QUERCETIN AND QUERCETIN PENTAACETATE ANALOGUE AGAINST C6 RAT GLIOMA CELLS

Saul V. S. Silva (PG)[1]*, Érica N. Soares (PQ)[3], Jessica T. de Souza (PQ)[3], Orlando M. Barboza ((IC)[2], Silvia L. Costa (PQ)[3], Victor D. A. da Silva (PQ)[3], Lourenço L. B. de Santana (PQ)[2], Aníbal de F. Santos Júnior PQ)[1,2].

Background: Quercetin is a flavonoid with antioxidant action and arise interest like a potential anticancer agent to use in glioma1. The low water solubility and the extensive metabolism associated with limited bioavailability reduce the biopharmacological use of this molecule2. **Objectives:** This work proposed to perform a structural modification in the quercetin molecule aiming obtain the analogue quercetin pentaacetate, improving the action of this flavonoid inhibiting growth cell rat glioma C6. **Methods:** The pentaacetyl analog was obtained after quercetin molecular modification2. The product was characterized by IR and 1H and 13C NMR spectroscopy. C6 glioma cells were cultured until confluence in in Dulbecco's modified Eagle's medium (DMEM) and were maintained in a humidified atmosphere composed of 95% air and 5% CO2 at 37 °C. The C6 cells cultures were treated with synthesized derivative pentaacetate and quercetin at different concentrations (50µM; 7 1:2 dilutions). The evaluation of cytotoxic activity was performed by

the 3-4,5-dimethylthiazol-2-yl, 2,5-diphenyltetrazolium bromide (MTT) assay. The effect of quercetin and pentaacetyl analogue compounds were analyzed after 24, 48 or 72 h. **Results:** The product was obtained in 1,3340g (62% yield) as a yellow solid with a melting point range of 178 – 186°C2. FTIR analysis demonstrating the replacement of hydroxyl groups by acetyl groups compatible with described in the literature2. NMR 1H and 13C analysis showed total acetylation with disappearance hydroxyl singlets in 1H NMR spectrum and arise of five large and characteristic signals of methyl in the aliphatic regions in 13C NMR spectrum like described in literature2. The MTT assay showed that Quercetin and the derivative petaacetate inhibit viability in 50% of C6 culture (IC50) at 50 µM and 11 µM respectively. The pentaacetyl compound showed to induce the glioma C6 cells to a rounded morphology, unlike quercetin, which induced to a fusiform filamentary morphology. **Conclusions:** Quercetin pentaacetate was able to inhibit glioma culture growth in a concentration and time dependent. The synthesized compound promoted a change in C6 morphology culture, for an unprecedented rounded profile. Therefore, these results can help in performance biological tests in several cells of neural and cancerous lineages, especially in glioma C6 cells.

Keywords: Quercetin, structural modification, glioma

BRAIN STABILITY IN PAIN?

Thaise Graziele L. de O. Toutain, Guzmán Alba, José Garcia Vivas Miranda, Raphael Silva do Rosário, Miguel Muñoz, Eduardo Pondé de Sena.

Programa de Pós-graduação em Processos Interativos dos Órgãos e Sistemas – PPgPIOS, Instituto de Ciências da Saúde – ICS, Universidade Federal da Bahia – UFBA.

Background: Pain is an alert signal of the organism, indicating that there is some threat, internal or external. Emotions can modulate pain and alter our brain activity, especially if they are pleasant. **Objectives:** Using brain functional networks (BFNs), the goal was to evaluate the topological stability of brain activity in the thermal pain induction, during the viewing of pleasant, unpleasant, neutral and black screen images. **Material and Methods:** This study followed the recommendations of the Declaration of Helsinki and was approved by the ethics committee of the Medical School of the Granada University (GU) – Spain, under No. 201302400001677. The images used were chosen through the International Affective Pictures System (with Spanish validation). Forty healthy GU students participated in this study, 20 males and 20 women (age range 18 – 28 years). Data collection was performed with a 65-channel electroencephalograph; Cz was used as reference; sample rate 1000Hz and impedance below 50 kOhm. After collection, we filtered the data, removed artifacts automatically, and used 56 electrodes for evaluation. We built the BFNs (1 minute), using time-varying graphs (TVG) and motifs synchronization methods, for each emotion, from each volunteer, with and without pain, through MATLAB®. **Results and Conclusion:** Through repeated measures ANOVA, we found increased brain connectivity during the painful condition ($p=0.001$), evaluated through the weighted degree. The frontal, central, left temporal and parietal regions increased connectivity during neutral and black screen visualization, independent of the painful condition. We used the clustering index and the number of edges of the BFNs to assess brain stability. We observed an increase in stability during the painful condition, which showed less variation for network topology and number of edge ($p<0.001$, in both comparisons). Interactions between "pain versus emotions" showed no significant differences for the indices studied, indicating that these indices may not have been sensitive enough to elucidate the modulation of pain by emotions. However, was observed to increase brain connectivity and stability during the pain.

Keywords: Brain Functional Network, Time Varying Graphs, Brain Stability, Pain Affective Modulation

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ANTIGLIOMA EFFECTS OF APOCAROTENOID 9'CIS-BIXIN FROM *BIXA ORELLANA* L.

Freitas, V.S.[1]; Cerqueira de, M.D.[2]; Velozo, E.S. [2]; Costa, M.F.D.[1]; El-Bachá, R.S.[1], Costa, S.L.[1]

[1] Laboratory of Neurochemistry and Cell Biology, ICS/UFBA; [2] Department of Organic Chemistry, UFBA; [3] Research Laboratory in Materia Medica, UFBA.

Background: Glioblastomas are the most common and lethal primary cerebral tumors. In recent years, no advance in therapeutics was able to assure a significant increase in the median survival of patients. The necessity to give new perspectives in glioma therapy stimulated the development of new drugs and innovations. Screening studies, especially those with polyphenolic compounds have grown significantly in recent years. In this work, we studied the toxicity to glioma cells of the apocarotenoid 9';cis-bixin, purified from the seeds of *Bixa orellana* L., known as Urucum, a plant found in the North and Northeast areas of Brazil. 9'cis-bixin (1.5 to 250 µM) cytotoxicity to U251 human glioblastoma, C6 murine glioma cells, and to primary normal astrocytes, derived from the brain of newborn Wistar rats, was measured by the MTT test 24 h and 72 h after treatment. Data were fitted to nonlinear regression plots to determine the concentration that kills 50 % of cells (EC 50). The type of cell death was determined by Annexin V / Propidium iodide staining and flow cytometry, after 72 h treatment with 75 µM The 9'cis-bixin killed cells, in a dose-dependent manner, with EC 50 of 0.55 µM, 0.56 µM, and 1.5 µM for U251, C6 and astrocyte, respectively. Moreover, treatment with of 9';cis-bixin for 72 hours, revealed that the carotenoid induced necrosis in 18.4% of U251 cells and apoptosis in 51.3% of C6 cells, with no significant effect in astrocytes. The data obtained indicate the cytotoxic potential of 9'cis-bixin in tumoral lines (U251 and C6) and lower toxicity to normal astrocytes and could be considered to future studies to better determine its antiglioma property.

Keyswords: glioblastoma, antitumoral, Bixin

Support: CNPq, FAPESB

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Universidade Federal da Bahia
Instituto de Ciências da Saúde
Av. Reitor Miguel Calmon s/nº
40.110-100 Salvador, BA – Brasil

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