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O prêmio José Ribeiro do Valle, oferecido a cada ano pela SBFTE, visa identificar a cada ano os melhores trabalhos científicos desenvolvidos por jovens investigadores na área da Farmacologia. Entre os trabalhos inscritos para esta décima-sexta edição do prêmio, foram selecionados cinco finalistas, que fizeram apresentações de seus respectivos trabalhos perante comissão julgadora, em sessão pública durante o 46º Congresso Brasileiro de Farmacologia e Terapêutica Experimental, em Fortaleza, CE. O resultado foi o seguinte:

Primeiro prêmio

Jhimmy Talbot

04.108 Smoking-induced rheumatoid arthritis aggravation is dependent of aryl hydrocarbon receptor activation and is influenced by genetic polymorphism. Talbot J[1], Liew FY[2], Peres RS[1], Pinto LG[1], Oliveira RDR[1], Silva JR[1], Lima KWA[1], França RFO[1], Ryffel B[3], Cunha TM[1], Alves-Filho JCF[1], Louzada-Júnior P[1], Cunha FQ[1] [1]FMRP-USP – Pharmacology, [2]University of Glasgow, [3]CNRS

Introduction: Rheumatoid Arthritis (RA) is an autoimmune disease with unknown etiology that affects 1% of worldwide adult population. RA is characterized by joint pain, intense immune cells infiltration into the joints and bone and cartilage destruction. It have been described that genetic and environmental factors are associated to RA susceptibility. Cigarette smoking is the major environment risk factor related to increase RA development and severity. However, the mechanism of smoking-induced RA aggravation is unknown. The aim of this research was to identify this mechanism. **Methods**: Experimental arthritis was accessed by mBSA-induced arthritis (AIA) in WT, *Ahr* or *Il-17a* genetic-deficient mice (*Ahr*KO or *Il-17a*KO); and by collagen-induced arthritis (CIA) [FMRP-USP Animal Ethics Committee (038/2009)]. Mice were exposed to cigarette smoke (CS) in a smoking machine. After arthritis induction we evaluated: articular hyperalgesia, neutrophil infiltration into joints, articular histopathology and CD4 + IL-17 + (Th17) frequencies. We also collected blood samples from RA patients and healthy controls to isolate gDNA for genotyping using TaqMan Probes and to evaluate Th7 frequencies by flow cytometry. [HCFMRP-USP Human Ethics Committee (2981/2009)]. **Results and discussion:** We found that exposure to CS increase the incidence, hasten disease rise and aggravates AIA and CIA, also increasing Th17 frequencies. We observed that CS extract can increase Th17 *in vitro* differentiation. Indeed, CS effects were not observed in *Il-17a*KO, suggesting that smoking-induced arthritis aggravation is dependent of effects on Th17 function. Among the components of CS, hydrocarbons are of particular interest since they are described as ligands of aryl hydrocarbon receptor (AhR), which in turn has been described as an important receptor to Th17 development. We observed that CS-induced increase of Th17 *in vitro* differentiation can be

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blocked by AhR antagonist CH223191. Moreover, treatment of mice with CH223191 inhibited CS-induced arthritis aggravation and Th17 increase. The loss of CS effects was also observed in *Ahr* KO mice showing that CS-induced arthritis aggravation is AhR/Th17-dependent. Interestingly, the hydrocarbons benzo [b]fluoranthen and ?-naptoflavone, present in high loads in CS, and the AhR agonist FICZ also increased Th17 *in vitro* differentiation and aggravated AIA. AIA aggravation induced by AhR agonist was lost in *Ahr* KO mice and was restored by transference of CD4 T cells from WT to *Ahr* KO. Further, we used a genetic association approach in humans with RA. We found an *AhR* genetic polymorphism (SNP; *rs2066853*) that increases AhR function and was related to higher Th17 frequencies in RA. Moreover, an interaction among the presence of this SNP and smoking increases the risk to RA (OR 2.66). Furthermore, smokers with this SNP are highly prone to show higher disease activity than non-smokers and present higher Th17 frequencies. **Conclusion**: Smoking (hydrocarbons in smoke) increase Th17 differentiation and aggravates arthritis through AhR activation. Moreover, genetic polymorphisms at *AHR* can influence smoking effects on arthritis development. **Financial Support:** Fapesp, CNPq, FAEPA, Capes

Segundo prêmio

Priscila de Souza

06.043 **Impaired vascular function in sepsis-surviving rats: evidence for endothelial dysfunction mediated by angiotensin II, increased ROS/RNS Generation and augmented activity of RHO-kinase**. de Souza P[1], Scheschowitsch K[2], da Silva LM[1], Guarido KL[2], Werner MF[1], Assreuy J[2], da Silva-Santos JE[2] [1]UFPR – Pharmacology, [2]UFSC – Pharmacology

Introduction: Several epidemiological studies reveal that the mortality rate among those who survive sepsis is strikingly higher when compared with age-matched people. We hypothesized that impairment of vascular function contribute to this higher mortality rate. **Methods:** Male Wistar rats were subjected to cecal ligation and puncture to induce sepsis (mortality rate ~ 30%). The isometric responses of aortic rings from survived animals were tested in organ baths at 30 or 60 days after (S30 and S60 groups, respectively). Functional and molecular changes were explored by Western blot and fluorescence techniques. The results obtained were compared with data from control (CT) rats; authorization from CEUA/UFPR: 527. **Results:** The effects of KCl, phenylephrine, angiotensin I, $CaCl_2$, acetylcholine and sodium nitroprusside were unchanged in aortic rings from S30 and S60 groups, compared with the CT. In contrast, angiotensin II (AII)-induced vasoconstriction was increased by 70% in aortic rings from S60 group. Interestingly, in opposite to vessels taken from CT rats, endothelium removal, incubation of L-NAME (100 µM) or losartan (1 mM), was unable to alter the contractile effects of AII in

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aortic rings from the S60 group. On the other hand, the NADPH oxidase inhibitor apocynin (1 mM), the O_2^- scavenger tempol (0.3 mM), and superoxide dismutase (SOD; 300 U/mL) fully avoided the enhanced responses to AII in the S60 group. When compared with the CT group, the activity of SOD in aortic homogenates of the S60 group was decreased by 45 ± 3%, while the generation of hydroperoxides lipids (LOOH) and glutathione (GSH) were increased by 41 ± 12% and 98 ± 3.9%, respectively. An increased ROS generation (up to 30%) was found in vessels from S60 rats after AII-stimulation, as detected by the fluorescent probe DHI. Importantly, immunofluorescence approaches revealed increased levels of tyrosine nitration (up to 70%), when compared to CT vessels, indicating exacerbated peroxynitrite production in vessels from the S60 rats. In addition, aortic rings from the S60 group presented a rightward shift of the concentration-response relaxation curve induced by the Rho-kinase (ROCK) inhibitor Y-27632 – EC50 of 0.43 (0.33-0.55) versus 1.03 (0.76 – 1.40) μM, in CT and S60 groups, respectively. Moreover, incubation with 0.3 μM Y-27632 reduced by 60% the effects of AII in aortic rings from CT, but was completely ineffective against AII-induced contraction in vessels from the S60 group. Western blot analysis revealed that when compared with the CT, vessels from the S60 group presented increased levels of RhoA, ROCK II and the phosphorylated MYPT-1, the main target of ROCK, without changes in the expression of ROCK I and total MYPT-1. **Discussion:** Our study discloses that under stimulation by AII, aortic rings from sepsis-surviving rats display endothelial dysfunction mediated by increased production of O_2^-, which in turn reduces the bioavailability of NO and increases the formation of $ONOO^-$. This increased oxidative and/or nitrosative stress may enhance the calcium sensitization mediated by the RhoA-ROCK pathway, leading to increased contractile responses to AII. In conclusion, this is the first study demonstrating long-lasting changes in the vascular and endothelial function of sepsis-surviving rats. **Research support:** Capes and FAPESC (2012000367 and 201200078).

Menção Honrosa

Jessica Barbosa do Nascimento Viana

01.003 LDT3 and LDT5: Pharmacological evaluation in human alpha-1 adrenoceptors. Nascimento-Viana JB[1], Alcántara-Hernández R[2], García-Sáinz JA[2], Romeiro LAS[3], Noël F[1], Silva CLM[1] [1]UFRJ – Farmacologia Bioquímica e Molecular, [2]UNAM – Fisiología Celular, [3]UnB – Desenvolvimento de Estratégias Terapêuticas

Zelia Menezes

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04.001 Microbiota is important to 5-fluorouracil-induced intestinal mucositis in mice. Menezes-Garcia Z[1], Arifa RDN[1], Acúrcio LB[1], Lima RL[1], Brito CB[1], Teixeira MM[2], Souza DG[1] [1]UFMG – Microbiologia, [2]UFMG – Imunologia e Bioquímica

Kátia Maciel Lima

04.022 cAMP elevating agents induce resolution of acute inflammation dependent on annexin A1. Lima KM[1], Caux TR[2], Vago JP[1], Tavares LP[3], Aribada RG[2], Carmo AAF[1], Galvão I[3], Costa BRC[2], Soriani FM[4], Perretti M[5], Silva PMR[6], Pinho V[1], Teixeira MM[3], Sousa LP[2] [1]UFMG – Morfologia, [2]UFMG – Análises Clinicas e Toxicológicas, [3]UFMG – Bioquímica e Imunologia, [4]UFMG – Biologia Geral, [5]QMUL, [6]Fiocruz – Fisiologia e Farmacodinâmica

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