PRÊMIO JOSÉ RIBEIRO DO VALLE 2019

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 vigésima primeira edição do prêmio, foram selecionados cinco finalistas, que fizeram apresentações de seus respectivos trabalhos perante comissão julgadora, em sessão pública durante o 51º Congresso Brasileiro de Farmacologia e Terapêutica Experimental, em Maceió, AL. O resultado foi o seguinte:

Primeiro prêmio

Douglas da Silva Prado

04.033 ERK5 mediates TGF-β signaling and shapes autoimmune inflammation. Prado DS, Damasceno LEA, Ferreira RG, Rosa MH, Cunha TM, Cunha FQ, Ryffel B, Waisman A, Alves-Filho JC FMRP-USP

Introduction: ERK5 is an atypical member of MAPK family that also exerts noncanonical functions such as act as a scaffold protein or co-transcription factor. It has been shown that TGF-β signaling in fibroblasts, hepatocytes and epithelial cells leads to ERK5 phosphorylation, which induces ERK5 activation. In line, it is very well established that TGF-β is critical for Treg and Th17 cell differentiation, being important to control autoimmune response. Thus, we hypothesized that ERK5 could modulate Treg and Th17 cell differentiation, playing a key role in the fate of autoimmunity. **Aim:** to evaluate the role of ERK5 on CD4 T cell differentiation and experimental autoimmune encephalomyelitis (EAE) development. **Methods:** CD4 naïve T cells purified from C57BL/6, $ERK5^{flox/flox}$ or $CD4^{cre}ERK5^{flox/flox}$ mice were cultured under Treg- or Th17-cell polarizing conditions (TGF-β and TGF-β+IL-6, respectively) and then their differentiation was analyzed by flow cytometry, ELISA or qPCR. First, we checked pERK5 expression in Treg and Th17 in relation a control group without TGF- β. In order to check the role of ERK5 in Treg and Th17 differentiation, ERK5 pathway was blocked with different inhibitors, such as XMD 8-92 or ERK5-IN-1 (0,3, 1 or 3 μM; 0,1, 0,3 or 1 μM, respectively; ERK5 inhibitors). The contribution of ERK5 in the pathogenesis of autoimmune diseases was investigated by inducing a model of multiple sclerosis, called experimental autoimmune encephalomyelitis (EAE), which is induced by injection of MOG_{35-55} peptide subcutaneously. **Results:** we found that ERK5 phosphorylation is increased in Treg and Th17 cells when compared with control group (Th0, no cytokines), suggesting that TGF-β can increase pERK5 expression. Then, we showed that pharmacological inhibition or genetic deficiency of ERK5 in CD4 T cells decreased Treg cell differentiation, whereas Th17 polarization was enhanced. Interestingly, ERK5 inhibition or genetic deletion do not modulate Th17 differentiation when the cells are cultured in conditions without TGF-β, suggesting its role in ERK5 activation. In line, ERK5 phosphorylation leads to ERK5 nuclear translocation. Thus, we analyzed ERK5 expression in the nucleus of Treg and Th17 and we found the both cell types express ERK5 in the nucleus, while Th0 lacks ERK5 in the nucleus, suggesting a pivotal role of TGF-β in ERK5 nuclear translocation into the nucleus. Moreover, $CD4^{cre}ERK5^{flox/flox}$ mice developed more severe EAE than control $ERK5^{flox/flox}$ mice, characterized by an increase of clinical score and Th17 response by recall assay, as well as a reduction of Treg cells in draining lymph nodes. **Conclusion:** our study reveals a novel role of ERK5 in modulating Treg/Th17 cell differentiation and attenuating the severity of EAE. Therefore, ERK5 could be a potential therapeutic target for autoimmune diseases.

Segundo prêmio

Franciele Franco Scarante

03.005 **The anti-stress effects of the combination of Escitalopram and Cannabidiol in mice depends on anandamide levels in the prefrontal cortex**. Scarante, FF[1], Vicente MA[1], Fuse EJ[1], Lopes VD[2], Aguiar RP[3], Scomparin DS[1], Guimarães FS[1], Campos AC[1] [1]FMRP-USP, [2]FCFRP-USP, [3]UEM

The late onset of action antidepressants, such as the selective serotonin reuptake inhibitors (SSRIs) is one of the main limitations in the psychiatric practice. A possible strategy to overcome this limitation is to combine SSRIs with agents that could accelerate the efficacy of the treatment. Here, we hypothesized that the combination of the SSRI escitalopram (ESC) with a subeffective dose of the phytocannabinoid cannabidiol (CBD) would accelerate the behavioral and neuroplastic effects of the treatment in stressed mice. Male C57Bl6 mice (10-12 weeks old) were submitted to a 10-day protocol of repeated unpredictable or social defeat stress and were treated with Vehicle or ESC (10mg/kg) in combination with Vehicle or CBD (7.5mg/kg) during 7 days. While previous study from our group indicated that ESC alone would induce an anxiolytic-like effect at the dose of 20mg/kg after 14 days of treatment in stressed mice, our results have shown that combining half this dose with a subeffective dose of CBD induced an anxiolytic-like effect evidenced in the novelty-suppressed feeding test after only 7 days of treatment in stressed o animals. The ESC+CBD treatment also induced a significant increase in the expression of the pre-synaptic marker synaptophysin in the prefrontal cortex (PFC), indicating that the behavioral effects were accompanied by an increased synaptic plasticity in this region. Since the facilitation of the anandamide (AEA) signaling has been proposed as a response induced by both CBD and repeated ESC treatment, we addressed whether disrupting the synthesis of this endocannabinoid in the PFC would prevent the behavioral effects induced by the drug combination. In order to address that, mice were submitted to stereotaxic surgery to receive via intra-PFC a viral vector containing a construct that directs the CRISPR-Cas9-mediated deletion of the AEA synthesis enzyme N-acyl phosphatidylethanolamine-specific phospholipase D (NAPE-PLD). A construct containing a scramble sequence was injected via intra-PFC in the control wild-type (WT) mice. After 15 days of recovery, the animals were submitted to the 10-day repeated stress and 7-day treatment with the drug combinations. In the WT control group, as shown before, ESC and CBD, when combined, induced an anxiolytic-like effect. However, this effect was absent in the mice in which the expression of NAPE-PLD was deleted in the PFC, indicating that the deletion of AEA synthesis in the PFC prevents the anxiolytic-like effect of the combination of ESC and CBD in stressed mice. In conclusion, our results show that the AEA signaling in the PFC is required for the accelerated behavioral outcomes induced by the combination of ESC and CBD. Ongoing experiments are investigating the role of the signaling mediated by the endocannabinoid 2-arachidonoyl-glycerol (2-AG) in the response to the drug combination as well. CEUA number: 032/2015-1; CEUA number: 47/2019. Financial support: CNPq, FAPESP and L'Oreal Institute.

Menção Honrosa

Irismara Sousa Silva

04.008 **A novel platelet-activating factor and protease-activated receptor (PAR)-2 network in lung inflammation in mice.** Silva IS, Almeida AD, Lima Filho ACM, Braga WF, Capettini LSA, Leite JIA, Leite MF, Klein A UFMG

Natalia Barreto da Silva Ribeiro

04.012 **Therapeutic administration of gold nanoparticles (AuNPs) accelerates resolution of silica-induced lung fibrosis in mice**. Ribeiro NBS, Capelozzi VL, Silva VM, Machado MP, Sa YAPJD, Arantes ACS, Martins PMRS, Martins MA Fiocruz

Kassiano dos Santos Sousa

04.034 **Purinergic signaling converts N-acetylserotonin into the pineal darkness hormone.** Sousa KS, Quiles CL, Ferreira ZFS, Markus RP USP

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