PRÊMIO JOSÉ RIBEIRO DO VALLE 2016

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-oitava edição do prêmio, foram selecionados cinco finalistas, que fizeram apresentações de seus respectivos trabalhos perante comissão julgadora, em sessão pública durante o 48º Congresso Brasileiro de Farmacologia e Terapêutica Experimental e 21º Congresso Latino-Americano de Farmacologia, em Foz do Iguaçu, PR O resultado foi o seguinte:

Primeiro prêmio

Gabriela S Kinker

10.001 **Melatonin receptors as pharmacological targets for glioma therapy.** Kinker GS[1], Oba-Shinjo SM[2], Carvalho-Sousa CE[1], Muxel SM[1], Marie SKN[2], Markus RP[1], Fernandes PA[1] [1]IB-USP - Fisiologia, [2]FM-USP- Neurologia

Introduction: Gliomas, the most common primary brain tumors in adults, exhibit poor responses to standard treatment and are associated with high mortality. We have recently demonstrated that the ability of such tumors to synthesize/accumulate melatonin negatively correlates with their overall malignancy (Kinker et al., J Pineal Res, 60, 84, 2016). Using luzindole, a non-selective antagonist of melatonin membrane receptors, we have shown that glioma-synthesized melatonin exerts an autocrine anti-proliferative effect. Additionally, based on The Cancer Genome Atlas (TCGA) glioma RNAseq data, we have designed a two-gene predictive model of the content of melatonin in the tumor microenvironment, combining the gene expression levels of melatonin synthesis and metabolism enzymes. The ASMT:CYP1B1 index negatively correlates with tumor grade and represents an independent prognostic factor: a low score, suggestive of reduced melatonin, is strongly associated with poor survival. Therefore, to further characterize the pathophysiologic relevance of the melatonergic system of gliomas, here we investigated the specific roles of melatonin receptors MT1 and MT2 in the oncostatic actions of this indolamine. **Methods**: We evaluated the expression of melatonin membrane receptors, MT1 and MT2, in human glioma cell lines with different grades of aggressiveness (HOG < T98G < U87MG), by imaging flow cytometry. Cell lines were treated with DH97 (10^{-10} – 10^{-6} M, 48 h), an MT2-selective antagonist (pKi = 8.03, 89-fold selectivity over MT1), and cell number was estimated by MTT assays. Using the TCGA RNAseq and clinical data of 624 patients, we evaluated the association between the overall malignancy of gliomas and the expression of MT1 and MT2 receptors. **Results**: All cell lines expressed MT1 and MT2 and, surprisingly, the selective blockage of MT2 receptors by DH97 10^{-8} M significantly reduced the growth of HOG and T98G, less aggressive cell lines which synthesize/accumulate more melatonin. Interestingly, this oncostatic effect was reverted, in a concentration dependent manner (DH-97 10^{-7} – 10^{-6} M), by the concomitant inhibition of both melatonin receptors. In fact, the treatment with DH97 10^{-6} M mimicked the effects of the non-selective antagonist luzindole and stimulated the growth of HOG and T98G (15% greater than control), suggesting that MT1 and MT2 have opposite roles in tumor progression. Accordingly, the TCGA RNAseq data analysis revealed that the expression of MT2 alone is more frequent in high-grade (30%) than in low-grade (15%) gliomas. More importantly, among patients with a high ASMT:CYP1B1 index score, those expressing only MT1 presented a decreased expression of cell cycle progression genes and survived 1.7 times longer than those expressing only MT2. Conclusion: Overall, our data reinforce the prognostic value of the melatonergic system of gliomas, supporting further

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investigations of the biological relevance of tumors-synthesized melatonin. Additionally, we lay a substantial groundwork for the use of melatonin analogous that activate MT1 and/or inhibit MT2 receptors in glioma therapy. **Financial support**: FAPESP (2010/52687-1, 2013/13691-1, 2014/27287-0), CNPq (480097/2013-5, 162670/2014-1).

Segundo prêmio

Isadora Ramos de Andrade

01.024 **Obese adipose tissue contributes to increase proliferation, migration and** invasion **in breast cancer cells.** Andrade IR[1], Renovato-Martins M[1], João JA[2], Matheus ME[2], Silva SV[1], Bouskela E[1], Souza AP[2], Cláudio-da-Silva C[2], Barja-Fidalgo TC[1] [1]UERJ , [2]UFRJ

Introduction: Obesity is characterized by a chronic low-grade inflammation and is a major problem of public health, especially because of its association with several diseases, including cancer. Many studies have shown a higher incidence and a worse prognosis of breast cancer in obese women. Aiming to evaluate the influence of adipose tissue on tumor cells during obesity, we used an experimental model, in vitro, in which the conditioned media of cultures of adipose tissue (AT) explants of obese and non-obese individuals were used to stimulate two cell lines of human breast adenocarcinoma, MCF-7 and MDA-MB-231 (more metastatic than MCF-7). We have evaluated the influence of factors secreted by AT on the behavior of these cells, and the molecular mechanisms involved in those effects that could contribute to a worse prognosis in cancer. **Materials and Methods**: Tumor cells were stimulated with 20% of conditioned medium (CM) or with microparticles (MP) derived from A Texplants obtained from obese patients or lean individuals. In some experiments anti-MIP-1α or anti-VEGF were added to AT explant cultures. Cell viability (24 and 48 h stimulation) was assayed by MTT method; Cell cycle assay (24 h) was evaluated in flow cytometry; Cell migration assayed by wound healing method after 24 h stimulation; For tubule genesis assays on MatriGel, endothelial cells (HMEC) were incubated with the supernatant of cultures of tumor cells treated (24 h) with the conditioned medium obtained from obese or lean AT. Cell invasion was assessed through transwell migration after 24 h of stimulation. MMP9 RNA expression was evaluated by real-time PCR. **Results**: The MCF-7 cells, but not MDA-MB-231 cells, when stimulated with CM-or with MP-derived from obese AT showed higher proliferation ($p < 0.05$), compared to cells treated with CM- or MP- derived from lean AT. When anti-MIP-1α was added to obese AT explant cultures, the increasing proliferative effect of CM, but not of MP, was impaired in MCF-7 cells. On the other hand, CM and MP from obese AT enhanced the migration capacity of MDA-MB-231 cells ($p < 0.005$), but not of MCF-7 cells. The treatment of MDA-MB-231 cells with CM or with MP from obese AT explants enhanced their ability to induce tubulogenesis ($p < 0.01$) and invasion ($p < 0.05$). Both effects were blocked when anti-VEGF was added to obese AT explant cultures ($p < 0.005$). Furthermore, MP derived from obese AT increased ERK phosphorylation inMCF-7 cells ($p < 0.05$), whereas increased AKT phosphorylation in MDAMB-231 cells ($p<0.05$). **Conclusion**: Our results demonstrated that MP and molecules secreted by obese adipose tissue, like MIP-1α, VEGF, can improve the functionality of breast tumor cells, increasing proliferation, migration, invasion and their angiogenic properties, what might contribute to enhance malignancy. **Financial support**: CAPES, CNPq, FAPERJ This study was approved by Ethic Committee from Pedro Ernesto hospital (CAAE 36880914.0.0000.5259).

Menção Honrosa

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Davidson Furtado Dias

04.048 Atypical chemokine receptor ACKR2 contributes to the development of lung fibrosis in silicotic mice. Dias DF[1], Correa AMC[1], Pereira JG[1], Arantes ACS[1], Cordeiro RSB[1], Graham G[2], Martins MA[1], Silva PMR[1] [1]Fiocruz - Inflammation, [2]University of Glasgow - Infection, Immunity and Inflammation

Douglas Almeida

05.046 **Diabetic neuropathy is modulated by cannabinoid and opioid systems in obese mice.** Almeida D[1], Freitas Lima LC, Valadares WCP, Quintão JL[2], Silva JF[3], Romero TRL[2], Santos SHS [1]ICB-UFMG - Fisiologia e Farmacologia, [2]ICB-UFMG - Farmacologia, [3]ICB-UFMG - Fisiologia e Biofísica

Flávio Protásio Veras

04.041 **Pyruvate kinase M2 (PKM2), an isoenzyme of the glycolytic pathway, is pivotal to the development of psoriasis.** Veras F[1], Prado D[1], Melo B[1], Tartari P[1], Melo P[1], Costa L[2], Cecilio N[1], Publio G[1], Alves M[3], Lima D[4], Nakaya H[4], Sales K[3], Souza C[2], Cunha FQ[5], Alves-Filho JC[5] [1]FMRP-USP - Farmacologia, [2]FMRP-USP - Clínica Médica, [3]FMRP-USP - Biologia Celular e Molecular, [4]FCF-USP - Análises Clínicas e Toxicológicas, [5]CRID-FMRP-USP

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