Adenosine A_{2A} and dopamine D_2 GPCR heteromers in neuroendocrine lung carcinoids

M. Cavic[1], E. Moreno[2,3], M. Velinovic[4], Z. Bukumiric[5,] A. Krivokuca[1], J. Stojsic[6], E. Canela[2,6], V. Casado[2,3]

[1]Department of Experimental Oncology, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia; [2]Department of Biochemistry and Molecular Biomedicine, Faculty of Biology, University of Barcelona, Barcelona, Spain; [3]Institute of Biomedicine of the University of Barcelona (IBUB), Barcelona, Spain; [4]Clinic for Pulmonology, Clinical Center of Serbia, Belgrade, Serbia; [5]Department of Statistics, Faculty of Medicine, University of Belgrade, Serbia; [6]Service of Pathology, Clinical Center of Serbia, Belgrade, Serbia; [6]Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain

Introduction: Neuroendocrine tumors (NETs) of the lung represent a heterogeneous group of lung tumors with different prognosis and treatment options. Adenosine and dopamine receptors have been recognized as potential targets for the treatment of NETs [1,2]. The aim of this study was to evaluate the differences in genetic and protein expression and in the heteromerization of $A_{2A}R$ and D_2R G protein coupled receptors in neuroendocrine carcinoids of the lung and to correlate them with patient and tumor characteristics, therapy response and disease recurrence.
Methods: The patient group consisted of 26 typical (TC) and 26 atypical (AC) lung NET patients who undervent surgical treatment. Evaluation of genetic expression of $A_{2A}R$ and D_2R was performed by qRT-PCR, and protein expression by Western blot on the Odyssey Infrared Imaging System, from FFPE samples. Detection of $A_{2A}R$-D_2R heteromers was performed by Proximity ligation assay using the Duolink II *in situ* PLA detection Kit. Survival analysis was performed using the Kaplan-Meier product limit method; median with corresponding 95% confidence interval (95%CI) was used for description and the Log-rank test for the analysis of difference. Two-sided p values <0.05 were considered as statistically significant.
Results: $A_{2A}R$ protein expression was significantly higher in AC than TC samples (1.06 vs. 0.51, p=0.046). While no $A_{2A}R$-D_2R heteromers were detected in TC samples, 80% of AC samples showed marked $A_{2A}R$-D_2R heteromerization. No other molecular parameters were found to independently correlate with demographic and clinical data or patient survival.
Conclusion: The observed differences in the expression and heteromerization of $A_{2A}R$ and D_2R might be further explored for the design of bivalent heteromer-specific compounds useful for imaging as well as targeted/immunotherapy in lung NETs [3-5].

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