ADENOSINE RECEPTOR A3: ROLE AND EXPRESSION IN HUMAN THYROID CANCER

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A3 adenosine receptor (A3AR) agonists have been reported to influence cell death and survival. Interestingly, the A3AR is highly expressed in tumor compared to normal cells, which may justify A3AR as potential target for tumor growth inhibition (1). TNF-related apoptosis-inducing ligand (TRAIL/Apo2L) is a member of the tumor necrosis factor family of cytokines that can trigger apoptosis in susceptible cells by its cell-membrane death receptors TRAIL-R1 (DR4) and TRAIL-R2 (DR5) (2). In this study, we examined first the expression of A3AR in normal and pathological human thyroid tissues by immunohistochemistry. A3AR is highly expressed on the cell surface of different types of thyroid carcinomas compared to normal tissue. However we did not observe any correlation between the expression of A3 receptor and the different degree of cells differentiation. We have then investigated the anti-proliferative activity of the A3AR agonist, 2-Cl-IB-MECA, against thyroid papillary (NPA) carcinoma cell line. We showed that 2-Cl-IB-MECA (10-20-40 μM) induced the cell cycle arrest of G0/G1 at 24 hours and in a concentration-dependent manner ($n=4$; $p<0.01$). Investigations in the molecular mechanism showed that A3 receptor stimulation reduced the basal levels of ERK1/2 phosphorilation and the expression of cyclin D1 and cyclin E ($n=4$; $p<0.05$). Finally, 2-Cl-IB-MECA treatment (20μM) for 4 h before adding TRAIL (0.5-1-2.5 ng/ml) enhanced TRAIL-induced apoptosis in NPA cells as determined by propidium iodide (PI) staining ($n=5$; $p<0.001$). These data was confirmed by measuring the increased caspase-3 activity and poly-ADP-ribose-polymerase (PARP) cleavage ($n=4$; $p<0.01$).
Although the possible mechanism/s of this potentiation remain to be elucidate, these data suggest a promising therapeutic agent, 2-Cl-IB-MECA, for multimodal approaches to the treatment of thyroid cancers.

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2 Mitsiades N, Poulaki V, Tseleni-Balafouta S, Koutras DA, Stamenkovic I., (2000) Cancer Res. 60: 4122-4129.