ADENOSINE RECEPTORS IN COLON CARCINOMA TISSUES AND COLON TUMORAL CELL LINES: FOCUS ON THE A_3 ADENOSINE SUBTYPE

Stefania Gessi[1], Stefania Merighi[1], Katia Varani[1], Eleonora Fogli[1], Valeria Sacchetto[1], Annalisa Benini[1], Prisco Mirandola[2], Edward Leung[3], Stephen Mac Lennan[3], Carlo Feo[4], and Pier Andrea Borea[1]

[1]Dpt of Clin. and Exp. Med., Pharmacol. Unit and ICSI, University of Ferrara, Italy; [2] Dpt of Human Anat., Pharmacol. and For. Med., University of Parma; [3]King Pharm. Res. and Dev., Inc., Cary, North Carolina, [4] Dpt of Surg., Anesthes. and Radiol., University of Ferrara

Adenosine may affect several pathophysiological processes, including cellular proliferation, through interaction with A_1, A_{2A}, A_{2B} and A_3 receptors. In this study we characterized adenosine receptors in human colon cancer tissues and in colon cancer cell lines Caco2, DLD1, HT29. mRNA of all adenosine subtypes was detected in cancer tissues and cell lines. At a protein levels low amount of A_1, A_{2A} and A_{2B} receptors were detected, whilst the A_3 was the most abundant subtype in both cancer tissues and cells, with a pharmacological profile typical of the A_3 subtype. All the receptors were coupled to stimulation/inhibition of adenylyl-cyclase in cancer cells, with the exception of A_1 subtype. Adenosine increased cell proliferation with an EC_{50} of 3-12 μM in cancer cells. This effect was not essentially reduced by adenosine receptor antagonists. However dypiridamol, an adenosine transport inhibitor, increased the stimulatory effect induced by adenosine, suggesting an action at the cell surface. Addition of adenosine deaminase makes the A_3 agonist 2-chloro-N6-(3-iodobenzyl)-N-methyl-5'-carbamoyladenosine (Cl-IB-MECA) able to stimulate cell proliferation with an EC_{50} of 0.5-0.9 nM in cancer cells, suggesting a tonic proliferative effect induced by endogenous adenosine. This effect was antagonized by 5-*N*-(4-methoxyphenyl-carbamoyl)amino-8-propyl-2(2furyl)-pyrazolo-[4,3e]-1,2,4-triazolo [1,5-c] pyrimidine (MRE 3008F20) 10 nM. Cl-IB-MECA-stimulated cell proliferation involved extracellular-signal-regulated-kinases (ERK1/2) pathway, as demonstrated by reduction of proliferation with 1,4-diamino-2,3-dicyano-1,4-bis-[2-amino-phenylthio]-butadiene (U0126) and by ERK1/2 phosphorylation. In conclusion this study indicates for the first time that in colon cancer cell lines endogenous adenosine, through the interaction with A_3 receptors, mediates a tonic proliferative effect.