ADENOSINE RECEPTORS AND TUMORS: NEW PHARMACOLOGICAL TARGETS?

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Adenosine displays contradictory effects on cell growth: it improves cell proliferation, but it may also induce apoptosis and impair cell survival. Adenosine has been linked to tumour development. In particular, increased adenosine concentration has been reported inside tumoral masses. However, it is known that adenosine acts as cytoprotective agent during ischemic damage in brain and heart. This communication will elucidate how adenosine could exert contradictory effects on cell proliferation, survival and death by simultaneous stimulation of different cellular adenosine receptors, termed A_1, A_{2A}, A_{2B} and A_3. Following the pharmacological characterisation of adenosine receptor expression on the human melanoma cell line A375, we chose A375 as our cellular model to define how the extracellular adenosine signals are conveyed from each receptor. By using selective adenosine receptor agonists or antagonists, we found that A_{2A} stimulation reduced cell viability and cell clone formation while at the same time it improved cell proliferation. In support of this finding we demonstrate that the stimulation of A_{2A} adenosine receptors stably expressed in CHO cell clone reproduced deleterious effects observed in human melanoma cells. A_3 stimulation counteracted A_{2A}-induced cell death but also reduced cell proliferation. Furthermore, we found that A_3 stimulation ensures cell survival. We demonstrate that adenosine triggers a survival signal via A_3 receptor activation and it kills the cell through A_{2A} receptor inducing a signalling pathway that involves protein kinase C (PKC) and mitogen-activated protein kinases (MAPKs).