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> A2B functions as a cell death priming mechanism downstream of p53

'A Jack of all trades' is one phrase that has been used to describe p53, the most recently identified function of which has been the regulation of various aspects of cell metabolism, but is this regulation linked to the capacity of p53 to induce apoptosis? To answer this question, Kevin Ryan and colleagues re-examined their microarray data of potential p53 target genes for mRNAs that might be connected with metabolism. They selected the G protein-coupled adenosine receptor *ADORA2B* (which encodes A2B) as a potential candidate, and using cell lines that express inducible wild-type or mutant p53, verified that *ADORA2B* is a direct p53 target gene.

Various stimuli are known to induce p53 stabilization and activation, and some (cisplatin, ultraviolet (UV) light and methotrexate) but not all (γ-irradiation and 5-fluorouracil) resulted in the p53-dependent transcription of *ADORA2B*. Further experiments revealed that, in response to cisplatin, p53-mediated transcription of *ADORA2B* occurred in cells expressing the adenoviral *E1A* oncogene and did not occur in control cells. Overexpression of genes such as *E1A* can both transform cells and make them more sensitive to certain stimuli that induce apoptosis. These findings hinted that the expression of A2B might be linked to cell death. Further experiments showed that, in Saos-2 human osteosarcoma cells expressing a regulatable *ADORA2B* gene, A2B expression induced apoptosis, which was increased by treating the cells with an adenosine analogue, adenosine 5′-*N*-ethylcarboximide (NECA), an A2B ligand. Moreover, NECA–A2B-induced apoptosis was shown to be regulated by members of the BCL-2 family of pro-apoptotic and anti-apoptotic proteins, and the BH3-only pro-apoptotic protein PUMA in particular was required to induce apoptosis downstream of A2B expression.

The natural ligand of A2B is extracellular adenosine, which is generated by the breakdown of ATP and is released from cells under metabolic stress or which have increased energy consumption. As tumour cells are known to experience both states, and it is known that the extracellular fluid that surrounds tumours has increased levels of adenosine, the authors examined whether A2B expression could cause cells to respond to the production of extracellular adenosine. Under hypoxic (1% oxygen) conditions, which alter cell metabolism and induce cellular stress, HCT116 human colon cancer cells expressing exogenous A2B underwent apoptosis owing to the production of adenosine, the level of which was increased in the tissue culture medium of cells growing in hypoxic and not in normoxic conditions. The death of these cells was suppressed by PSB603, an A2B antagonist. As chemotherapy also induces stress and metabolic responses in cells, the authors examined whether A2B is involved in chemotherapy-induced death. Treatment with cisplatin of E1A-transformed mouse embryonic fibroblasts and the U2OS human osteosarcoma cell line resulted in an increase in extracellular adenosine, p53-mediated expression of A2B and induction of apoptosis, which could be blocked by PSB603.

The authors propose that A2B functions as a cell death priming mechanism downstream of p53 that responds to alterations in cellular metabolism that occur under stressful conditions and on exposure to some chemotherapeutic drugs.

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