Adenosine metabolism and cancer. Focus on “Adenosine downregulates DPPIV on HT-29 colon cancer cells by stimulating protein tyrosine phosphatases and reducing ERK1/2 activity via a novel pathway”

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ADENOSINE FACILITATES tumor survival by a variety of mechanisms. In this issue, Tan et al. (Ref. 16; see p. C433 of this issue) describe a signaling cascade by which adenosine downregulates the cell surface protein CD26 on HT-20 colorectal carcinoma cells. Because CD26 binds extracellular soluble adenosine deaminase (ADA) to the cell surface, this downregulation is expected to increase adenosine concentration in the microenvironment of the tumor cell membrane. This is one of several mechanisms by which tumors facilitate their own survival by influencing adenine nucleotide and adenosine metabolism and signaling.

Adenosine accumulates in solid tumors and stimulates tumor growth and tumor angiogenesis while imparting tumor resistance to the immune system (15). Part of this resistance is due to adenosine signaling through A2A and possibly A2B adenosine receptors to inhibit the activation of macrophages (9, 10) and lymphocytes (6). Imiquimod, an immune system activator with anti-tumor activity, has recently been shown to block A2A receptors (14). This is consistent with the notion that adenosine in tumors suppresses the immune system.

CD26 EXPRESSION IN TUMORS

While adenosine is generated as a result of hypoxia and necrosis in the core of tumors, there is emerging evidence that some tumors modify purine metabolism to facilitate production or retard degradation of adenosine. One such mechanism is the subject of the article by Blay and co-workers (16), featured on page C433 of this issue. These investigators and others have noted in previous studies that the cell surface protein, CD26, is downregulated in many cancers. In human (but not murine) cells CD26 serves as a binding protein for ecto-ADA, which in human colorectal carcinoma cells. Because CD26 binds extracellular soluble adenosine deaminase (ADA) to the cell surface, this downregulation is expected to increase adenosine concentration in the microenvironment of the tumor cell membrane. This is one of several mechanisms by which tumors facilitate their own survival by influencing adenine nucleotide and adenosine metabolism and signaling.

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Fig. 1. The influence of purine metabolism on tumor growth and survival. ATP in the extracellular space is cytotoxic to certain tumors due to activation of P2X receptors. ATP is degraded to adenosine (ADO), which can bind to the cell surface by CD26. In HT-29 colorectal carcinoma cells, Blay and coworkers (p. C433) show that adenosine inhibits the transcription and expression of CD26. High concentrations of adenosine in the tumor environment suppress T lymphocyte activation mediated by tumor antigen presentation on major histocompatibility protein (MHC) to T cell receptors (TCR) in part by signaling through adenosine A2A receptors (artwork by James A. Sullivan).
metabolism to adenosine. CD73 is one of several genes that are upregulated in radioresistant esophageal cancer cell lines compared with radiosensitive controls (4). CD73 protein is more highly expressed on prostate cancer cells than on normal prostate epithelial cells derived from the same patient (5). In a model of breast cancer, MDA-MB-435 cells with upregulated CD73 are prone to metastasize to lymph nodes (7). There is a dramatic overexpression of CD73 in estrogen receptor-negative breast cancer cell lines and in clinical samples (12).

ADENOSINE EFFECTS ON TUMOR CELLS AND ANGIOGENESIS

Adenosine also has direct effects to stimulate the growth of some tumors. Adenosine was found to be mitogenic for human breast carcinoma cells (8). Certain agonists and antagonists of A3 adenosine receptors have been reported to kill tumor cells, but some of these effects appear not to be receptor mediated. Another means by which adenosine may promote tumor survival is by stimulating angiogenesis. In macrophages, activation of the A2A receptor synergizes with some Toll-like receptors to increase the expression of VEGF (11), whereas activation of A2B and A3 receptors stimulate the release of VEGF and angiopoietin-2 from human mast cells (3).

In conclusion, a high concentration of adenosine in the core of solid tumors may facilitate tumor survival by suppressing the immune system and by facilitating angiogenesis. In addition, tumors may stimulate the conversion of purine nucleotides to adenosine by increasing the expression of CD73 or decreasing the expression CD26. Blay and co-workers show in this issue that adenosine per se reduces the expression CD26 on tumor xenografts: in vivo analysis of organ-specific metastasis. Int J Cancer 107: 528–534, 2003.

REFERENCES