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 impairing 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 cell 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, and, by localizing ADA to the cell surface, facilitates adenosine metabolism to inosine. Downregulating CD26 likely results in increased adenosine, especially near the cell surface. This could contribute to immune suppression in the tumor environment (Fig. 1). In their study, Blay and coworkers show that high levels of adenosine downregulate CD26 on the surface of HT-29 colorectal carcinoma cells, possibly resulting in the following positive feedback mechanism: decreased adenosine degradation → increased adenosine → decreased CD26 expression → decreased adenosine degradation. The downregulation of CD26 in tumor cells is correlated with increased protein tyrosine phosphatase and ERK activity and a decrease in CD26 transcription, although it is not clear that all of these effects are causally related. The downregulation of CD26 in response to adenosine is not significantly blocked by adenosine receptor antagonists, suggesting that CD26 regulation may not be mediated by G protein-coupled adenosine receptors, although it is possible that adenosine levels become high enough to overcome competitive receptor blockade.

ADENINE NUCLEOTIDE METABOLISM IN TUMOR HOSTS AND IN TUMORS

The downregulation of CD26 is one of several means by which cancer cells may elevate extracellular adenosine to promote tumor angiogenesis and escape immune surveillance. Extracellular nucleoside triphosphate diphosphohydrolases such as NTPDase-1 (CD39, apyrase, EC3.6.1.5) and ecto-5-nucleotidase (5-NT, CD73, EC3.1.3.5) together convert ATP to adenosine in the extracellular space. CD39, a B-cell activation marker, can hydrolyze either ATP or ADP, whereas CD73 hydrolyzes AMP to adenosine. CD39 activity not only contributes to adenosine formation, but also reduces ATP, which is cytotoxic to some tumors (2, 13). Animals may respond to tumors by inhibiting ATP metabolism. In rats inoculated with Walker 256 tumor cells, a reduction of ATP hydrolysis activity in serum and on platelets has been postulated to protect the host from tumor expansion by elevating ATP and reducing adenosine (1). On the other hand, some tumors enhance nucleotide

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metabolism to adenosine. CD73 is one of several genes that are upregulated in radiosensitive 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 human macrophages: role of NF-κB in A2A adenosine receptor induction. Biochem J 391: 575–580, 2005.

REFERENCES


