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Commentary

Adenosine in pancreatic cancer: Emerging combination therapies

Susanne Roth, Thilo Hackert*

Department of General, Visceral and Transplantation Surgery, Heidelberg University Hospital, Heidelberg, Germany

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Pancreatic cancer is one of the most aggressive malignancies with an extraordinarily poor prognosis and a mortality rate almost as high as its incidence. Currently, it is the 7th leading cause of cancer-related deaths worldwide, both in males and females [1], with a 5-year survival rate of about 9%. Due to the slow advancement in developing therapeutic interventions against this devastating disease as well as an increasing incidence, pancreatic cancer is projected to become the 2nd leading cause of cancer mortality before 2030 [2]. Multiple factors contribute to its dismal prognosis, including late-stage detection, early development of a systemic disease, and resistance against anti-tumour therapies. Nucleoside analogues such as gemcitabine, cytarabine, fludarabine, and cladribine are widely used for the treatment of multiple malignancies [3], and gemcitabine is the standard of care in pancreatic cancer patients with poor general condition, who cannot tolerate multi-agent chemotherapeutic regimens [4]. However, rapid induction of resistance, low response rates, and considerable side effects limit the usage of these drugs over longer durations, hence the development of new agents, identification of novel targets, and understanding of resistance mechanisms should take precedence to increase the abysmal survival rates of pancreatic cancer.

Adenosine, a naturally occurring nucleoside, which is increased in neoplastic microenvironments has been shown to have protumourigenic as well as anti-tumourigenic effects, depending on the receptors engaged on various cell types [5]. Adenosine is endogenously generated by de novo purine biosynthesis, s-adenosylhomocysteine hydrolysis, or metabolized from extracellular ATP by the ectonuleotidases CD39 and CD73, which is the major source of adenosine in the tumour microenvironment [5]. Nucleoside transporters in the cell membrane, including equilibrative nucleoside transporters (ENTs) and concentrative nucleoside transporters (CNTs), transfer extracellular adenosine into the intracellular compartment, limiting adenosine signaling via its cell surface receptors [5].

In a current study by Yang et al. in *EBioMedicine* the antitumour activity of adenosine is corroborated in pancreatic cancer [6]. The authors used both cell lines as well as pancreatic cancer mouse models to reach the conclusion that adenosine induces apoptosis and senescence in pancreatic cancer. They observed approximately 40% decrease in tumour volume after 6 weeks of adenosine treatment relative to controls in patient-derived xenograft mouse models. Mechanistically, adenosine seems to require its uptake into intracellular compartments through nucleoside transporters to induce apoptosis in pancreatic cancer cells. While pharmacological inhibition of the four transmembrane G protein-coupled adenosine receptors, A1a, A2a, A2b, and A3 did not impair the cytotoxic effects of adenosine in pancreatic cancer cell lines, blockade of ENT and CNT nucleoside transporters by dipyridamole, which leads to decreased intracellular adenosine levels, reduced its anti-tumour effectiveness. In pancreatic tumour cells, intracellular adenosine increased protein levels of p21, a cycle inhibitor that mediates cellular senescence. Downregulation of p21 by RNAi in combination with adenosine treatment further reduced tumour cell viability, presumably by switching cellular senescence to apoptosis. Consistently, inhibition of the serine/threonine kinase AKT, shown to induce senescence by promoting p21 and p53 accumulation [7], together with adenosine treatment synergistically augmented apoptosis of pancreatic cancer cell lines *in vitro* and in an orthotopic implantation tumour model *in vivo* [6].

Taken together, the authors conclude that adenosine has antitumour properties in pancreatic cancer by inducing apoptosis that is enhanced if cellular senescence is inhibited by blocking the AKT/p21 axis [6]. This study considerably advances our

* Corresponding author.
E-mail address: thilo.hackert@med.uni-heidelberg.de (T. Hackert).

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understanding of adenosine and its mode of action in pancreatic cancer. Earlier studies on adenosine as an anti-tumour agent mainly focused on cell lines, hence the effectiveness of adenosine in xenograft and orthotopic implantation tumour mouse models substantiate its anti-tumour activity *in vivo*.

However, a large body of evidence indicates that increased levels of adenosine in the tumour microenvironment can contribute to a cancer growth-promoting milieu, especially by immunosuppressive and angiogenic effects [5]. While adenosine accumulation upon acute tissue damage protects cells from immune-mediated deterioration by limiting inflammatory responses, chronically elevated adenosine levels, such as in the tumour microenvironment trigger and maintain an immunosuppressed niche [5]. Adenosine has been shown to primarily impair anti-tumour immune responses via signaling through G protein-coupled transmembrane receptors, restraining macrophage activation, natural killer cell and cytotoxic T cell functions [5,8]. Currently, novel drugs are being tested to prevent adenosine-mediated immunosuppression in human cancer within clinical trials, as single agents and in combination with immune checkpoint inhibitors [8]. Yet, so far the anti-tumour activity of adenosine in pancreatic cancer *in vivo* has only been shown in immunosuppressed mice [6], thereby neglecting potential immunosuppressive tumour-promoting side effects. Since adenosine seems to exert its tumour growth-inhibiting effects via intracellular mechanisms, but not through the engagement of cell surface receptors [6], combined treatments of adenosine with adenosine receptor inhibitors might induce apoptosis in cancer cells and prevent adenosine from acting as an immunosuppressant at the same time. Thus, an in-depth characterization of pro-and anti-tumourigenic effects of distinct adenosine receptor signaling pathways in different cell types in the tumour microenvironment in immunocompetent pancreatic cancer models is essential for developing combination strategies targeting the adenosinergic system. An important caveat to keep in mind is that adenosine also has effects, beyond the tumour microenvironment including the cardiovascular system. Currently, adenosine is an FDA approved drug for terminating paroxysmal supraventricular tachycardia involving the atrioventricular node [9], mediating its electrophysiological effects through cell surface receptors. In this regard, further in-depth studies are required to elucidate the mechanisms favoring its intracellular modes of action before adenosine can be considered as a drug candidate for anti-cancer therapy.

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