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Commentary **Open Access**

Adenosine A2B receptor: novel anti-cancer therapeutic implications

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Extracellular adenosine is a product of the metabolism of nucleotides such as ATP and ADP and mediates a wide range of events under normal and pathological conditions[1,2]. Adenosine receptors belong to the G-coupled signalling receptors and are broadly expressed in normal tissues in 4 subtypes (A1, A2A, A2B, A3).

While A2B has traditionally been considered of less relevance in comparison to A2A due to lower affinity of the ligand for this adenosine receptor subtype, recent evidence strongly suggests a specific role of this receptor in cancer and other pathological conditions[3,4].

The authors of this review are experts in the field of adenosine signalling. In this work they analyse the oncogenic role of the A2B receptor, also proposing and discussing its targeted blockade as a new anti-cancer therapeutic option.

As they explain, the mechanisms thought to be involved in A2B-mediated tumour progression are multiple. Adenosine is responsible for modulating the tumour microenvironment and the phenomenon of angiogenesis via production of growth factors, cytokines and chemokines. Also, it is involved in the regulation of dendritic cells and macrophages differentiation and function, aspects, these, crucial for tumour immune-surveillance. Lastly, via its A2B receptor, adenosine modulates the inflammatory response to the tumour and promotes tumour cells migration and therefore metastasis.

The effects of protracted inflammation can be devastating on normal tissues. Adenosine modulates inflammation by enhancing differentiation of T-regulatory and myeloid derived suppressor cells which are able to induce T-cells anergy[5]. Also, through its A2B receptor, adenosine induces anti-inflammatory cytokines such as IL-10, further limiting the amplification of the inflammatory biochemical cascade. On the other hand, activation of the A2B receptor can be associated with pro-inflammatory effects through activation of mast cells, fibroblasts and other epithelial cells, such as intestinal cells[6]. The pro- or anti-inflammatory action of adenosine has been subject to extensive study and debate through the recent years and it seems to be dependent on specific cell type and extracellular microenvironment[7,8].

Quick Response Code:

Phylogenetically, both the anti-inflammatory and the pro-inflammatory actions of adenosine have a protective function, the first keeping in check the cascade of events typical of inflammation and thus avoiding tissue damage, the second facilitating the reaction to and elimination of foreign pathogens.

Exactly as it is the case for other immune-checkpoints, tumour cells can exploit these defence mechanisms to induce immune suppression and cancer-tolerance. In this context, the expression of A2B in immune cells has attracted a lot of attention, as the receptor seems to drive the expansion of immunosuppressive, pro-angiogenic and cancer tolerant cells[9]. For these reasons, adenosine may be considered itself an immune-modulatory checkpoint molecule[10]. This hypothesis is further strengthened by evidence of a synergic anti-tumour effect elicited combining anti-PD-1 (or CTLA-4) and adenosine signalling inhibitors[11-14]. This synergism requires CD73 (one of the nucleotidases involved in adenosine generation) expression on tumour cells, suggesting that the adenosine produced in the context of the tumour could interfere with the effect of targeted immunotherapies[13]. The addition of A2A- or A2B-receptor inhibitors to current targeted immunotherapies could therefore represent a means to overcome acquired resistance to such treatments.

It is worth noting that, besides the effects of adenosine and A2B on the immune system, the expression of this receptor on the surface of cancer cells seems to mediate important oncogenic effects in a variety of cancers. Pharmacological inhibition or knockdown of A2B decreases proliferation of tumour cells[15-17] and a role for A2B in tumour progression and metastasis is supported by multiple studies in bladder, breast, colon, prostate and other cancers[14,15,18-20].

In particular in triple negative breast cancer, expression of CD73 is associated with poor prognosis and pharmacological resistance to doxorubicin[21]. Similarly, high expression of A2B in cancer cells increases invasiveness and metastasis and is a predictor of poor prognosis and shorter survival in triple negative breast cancer (TNBC)[19]. On the other hand, presence of A2B in the host immune cells does not impact the metastatic potential of TNBC tumour cells in the same metastatic mouse models of breast carcinoma, as demonstrated by the fact that blockade of tumour-expressed A2B receptor, in A2B receptor-deficient mice, reduces the metastatic burden from TNBC cell lines xenografts.

Moreover, constitutive activation of the adenosine receptor A2B in response to a hypoxic microenvironment has been associated with increased proliferation of prostate cancer cells *in vitro*[20].

Lastly, the A2B receptor has been shown to activate downstream oncogenic pathways frequently mutated in cancer such as mitogen-activated protein kinase[18,19], as well as phospholipase C, cathelicidin antimicrobial peptide, *NFkB1* and arachidonic acid signalling. Moreover, A2B is also a downstream target of the transcription factor *Fos-related Antigen-1* (*Fra-1*), a gene involved in the development of metastasis[16]. A2B pharmacological blockade in *Fra-1* positive breast cancer cells inhibited metastasis to the lungs in a mouse model of metastatic breast cancer. In the near future, it is possible that identification of *Fra-1* positive tumours will guide the stratification of patients that are most likely to respond to A2B inhibitors.

Notwithstanding the mounting evidence in favour of an oncogenic role for A2B, most of the data supporting this hypothesis come from pre-clinical studies *in vitro*. Whilst A2A small molecule inhibitors are already in clinical development (NCT02403193 and NCT02655822), the same cannot be said for A2B receptor inhibitors. All the A2B receptor inhibitors have been tested *in vitro* and *in vivo*, but their pharmacokinetic characteristics are still mostly unknown.

A2B has the potential to become a therapeutic target, at least in tumours overexpressing the protein. However, more studies are needed to explore all the functions of the A2B receptor and its ligand, particularly with the aim of gaining a better understanding of the multiple A2B receptor-independent metabolic effects of adenosine[22].

Moreover, due to the extensive cross-talk and the number of molecular targets involved with the adenosine signalling pathway, and considering the ubiquitousness of the receptors, it is conceivable that side effects of the inhibition of CD73, A2A and A2B could represent an issue in the clinical setting.

Finding strategies to specifically target receptors expressed on tumour cells could help mitigate the toxicity of these agents. Also, using these drugs in combination with other targeted agents, as it is already the case with A2A-inhibitors, will hopefully further decrease toxicities by exploiting the synergism shown in combination therapy.

Finally, pharmacologically modulating metabolic conditions such as hypoxia should likely increase the effectiveness of these molecules.

Accumulating knowledge of the adenosine signalling targets drives the identification of biomarkers and predictors of response/resistance, opening therefore the possibility of a personalised therapeutic approach.

DECLARATIONS

Authors' contributions

Concept and design of the article: S.P. Corona, N. Sobhani, D. Generali
Definition of intellectual content, literature search and manuscript preparation: S.P. Corona
Manuscript editing: S.P. Corona, D. Generali

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There are no conflicts of interest.

Patient consent

Not applicable.

Ethics approval

Not applicable.

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