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The double-edge sword effect of anti-CD73 cancer therapy

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We and others have identified CD73 as a new cancer target. I hereafter discuss that targeted blockade of CD73 has the effect of a "double-edge sword," able on the one hand to rescue endogenous adaptive anti-tumor immune responses, and on the other hand, inhibit the metastatic potential of tumor cells.

We have recently described a new strategy for breaking immune tolerance to cancer and prevent metastasis: by targeted blockade of CD73, the ecto-enzyme responsible for the hydrolysis of extracellular adenosine monophosphate (AMP) to adenosine.[1,2] Controlled release of triphosphate (ATP) and activation of purinergic receptors is now well-recognized as a ubiquitous means of intercellular communication that regulate key physiological functions such as neurotransmission, renal tubule-glomerular feedback, bone remodelling, ectopic tissue calcification, endothelial permeability and immune responses.[3] In the immune system, extracellular ATP acts as a "find-me signal" that guides phagocytes to inflammatory sites and promotes clearance of apoptotic cells. Extracellular ATP also acts as a co-activator of the NLRP3 inflammasome and a trigger of adaptive anti-tumor immunity, a mechanism essential to the therapeutic activity of certain chemotherapeutic drugs.[4] In contrast to extracellular ATP, extracellular adenosine is a potent immunosuppressor. The effects of extracellular adenosine on tumor immune surveillance was first revealed by Ohta et al.,[5] who demonstrated that transcriptional silencing of A2A adenosine receptors in T cells enhances their anti-tumor function in vivo.

Glycosyl-phosphatidylinositol-anchored CD73 is generally considered as the rate-limiting enzyme in the generation of extracellular adenosine.[3] CD73 is constitutively expressed at high levels in various types of cancers. We have recently set out to elucidate CD73's role in tumor immune evasion and metastasis and assess the activity of CD73-targeted therapy. In our first study, we injected immunocompetent and immunodeficient mice with pro-metastatic mouse breast tumor cells and treated the animals with anti-CD73 mAb.[1] We observed that inhibition of primary tumor growth with anti-CD73 mAb was dependent on an adaptive immune response, while suppression of lung metastasis was maintained in immunodeficient mice. This raised the possibility that CD73 intrinsically modulates tumor cell migration. Our in vitro studies revealed that tumor-derived CD73 promoted tumor cell chemotaxis via activation of A2B adenosine receptors.[1]

In addition of being expressed on various tumor cells, CD73 is expressed on endothelial cells, mesenchymal stem cells, Foxp3$^+$ T regulatory cells (Tregs) and subsets of leukocytes that form the tumor stroma. This suggests that non-transformed stromal cells may help tumor cells evade immunosurveillance through the production of extracellular adenosine. To address this question, we recently investigated the role of host-derived CD73 in tumor immune evasion.[2] Our work revealed that: (1) CD73$^-$deficient mice are resistant to the growth of immunogenic tumors in a CD8$^+$ T cell-dependent manner; (2) hematopoietic and non-hematopoietic CD73 expression each promote tumor immune escape in a non-redundant manner; (3) CD73 expression on Foxp3$^+$ Tregs is a key component in the pro-tumorigenic effect of Tregs; and (4) non-hematopoietic expression of CD73, presumably on endothelial cells, enhances tumor cell metastasis to the lungs.

Since our initial report, other groups have now demonstrated the anti-tumor activity of targeted CD73 blockade. Jin et al.[6] demonstrated the therapeutic effect of CD73 inhibition in a mouse model of ovarian cancer. The same group also recently demonstrated that CD73-deficient mice have increased CD8-dependent anti-tumor immunity and that non-hematopoietic and hematopoietic expression of CD73 promotes tumor growth in mice.[7] In their latter study, the authors demonstrated that tumor-bearing CD73-deficient mice have enhanced homing of tumor antigen-specific T cells to draining lymph nodes and tumors. The authors proposed that CD73-dependent extracellular adenosine limits tumor homing of tumor-specific T cells via the activation of A2B adenosine receptors. Yegutkin et al.[8] also recently reported that CD73-deficient mice have increased anti-tumor immunity.

Taken together, these studies provide good evidence that targeting CD73 can induce anti-tumor activity in mice. Nevertheless, additional experiments are needed before translating these findings

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Table 1. Summary of identified immunosuppressive and pro-metastatic effects of CD73

	Immunosuppressive effects	Pro-metastatic effects
CD73 on tumor cells	Inhibits the function of tumor-reactive CD8+ T cells via A2A adenosine receptors.	Enhances tumor cell invasion; enhances tumor cell chemotaxis via A2B adenosine receptors.
CD73 on Foxp3+ Tregs	Promotes tumor growth, presumably via inhibition of tumor-reactive T cells.	n/d
CD73 on endothelial cells	Blocks tumor homing of tumor-reactive T cells via A2B adenosine receptors.	Promotes lung metastasis of intravenously injected tumor cells.

n/d: not determined

into the clinic. First, extensive documentation of CD73 expression in various types of human cancers is needed. Second, evidence that targeting human CD73 with a therapeutic mAb induces anti-tumor activity is still pending. Third, in depth analysis of anti-CD73 mAb therapy mechanism-of-action is required. Finally, evaluation of the potential toxicities that may be associated with CD73 blockade is critical. CD73 is involved in several physiological systems and this could potentially limit anti-CD73 therapy. Studies in CD73-deficient mice have shown that CD73 is important for platelet aggregation and to protect the heart, kidney and lungs from ischemia.[9] Notably, a recent study identified mutations in the CD73 gene resulting in a non-functional protein and the development of symptomatic arterial and joint calcification in humans,[10] a pathology associated with an excess risk of cardiovascular events. The increase in ectopic tissue calcification associated with a non-functional CD73 protein was found to be dependent on an increase in tissue-nonspecific alkaline phosphatase (TNAP). Therefore, anti-CD73 mAb therapy could theoretically be combined with inhibitors of TNAP such as bisphosphonates or lansoprazole in order to prevent the risk of arterial calcification.

In conclusion, our recent work revealed that CD73 expression on tumor cells, non-hematopoietic and hematopoietic host cells, including Foxp3$^+$ Tregs, potently suppresse adaptive anti-tumor immune responses. We also observed that CD73 expression on non-hematopoietic host cells—possibly endothelial cells—enhances tumor cell metastasis to the lungs. These findings, now validated by other independent groups, strongly suggest that CD73 may be targeted at multiple levels to induce anti-cancer effects.

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