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Adenosine receptor 2A blockade increases the efficacy of anti-PD-1 through enhanced anti-tumor T cell responses

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Immunotherapy is rapidly emerging as a cancer treatment with high potential. Recent clinical trials with anti-CTLA-4 and anti-PD-1/PDL-1 antibodies (mAbs) suggest that targeting multiple immunosuppressive pathways may significantly improve patient survival. The generation of adenosine by CD73 also suppresses anti-tumor immune responses through the activation of A2A receptors on T cells and NK cells. We have previously shown that blockade of A2A receptors can suppress tumour metastasis (1) and enhance responses to anthracycline therapy (2). Since A2A expression is enhanced on T cells following their activation, we hypothesised that A2A blockade would enhance the efficacy of anti-PD-1 mAb, an immunotherapy which acts through the liberation of anti-tumour immune responses.In the current study (3), we observed that the expression of CD73 by tumor cells limited the efficacy of anti-PD-1 mAb in two tumor models and that this was alleviated with concomitant treatment with an A2A adenosine receptor antagonist. The specificity of this effect for the A2A receptor was confirmed with the use of A2A knockout mice. The blockade of PD-1 enhanced A2A receptor expression on CD8+ tumour-infiltrating T cells, making them more susceptible to A2A mediated suppression. Thus, dual blockade of PD-1 and A2A significantly enhanced the expression of IFNγ and Granzyme B by tumor-infiltrating CD8+ T cells and accordingly, increased growth inhibition of CD73+ tumors and survival of mice. Moreover, A2A blockade was found to enhance the ability of PD-1 and TIM-3 to treat established 4T1.2 tumor metastases.Our study indicates that CD73 expression may constitute a potential biomarker for the efficacy of anti-PD-1 mAb in cancer patients and that the efficacy of anti-PD-1 mAb can be significantly enhanced by A2A antagonists. A2A antagonists, including SYN115 as utilized in our study, have undergone phase II trials for Parkinson's Disease and have been shown to be safe and well tolerated. Thus, this approach has high translational potential for the treatment of cancer patients.

Biography

Paul A Beavis completed his PhD at Imperial College London, studying the biology of regulatory T cells in rheumatoid arthritis. He is currently a senior Post-Doc in Assoc. Prof. Phil Darcy's Immunotherapy Group at the Peter MacCallum Cancer Centre. His current work is focused upon the application of combination immunotherapies and the use of chimeric antigen receptor transduced T cells to treat Breast Cancer. His workis already been published in PNAS, Trends in Immunology, OncoImmunology and the work presented in this meeting is currently under review at Cancer Immunology Research.

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