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ABSTRACT

Melanoma is a malignant cancer of skin, mucous membranes and uvea which originates from melanocytes and characterizes in high mortality. CD73 is an enzyme producing extracellular adenosine. Because of its participation in stimulation of tumor angiogenesis, metastasis and regulation of immune response to cancer, CD73 can be a new potential therapeutic target.

The aim of this thesis was analysis of the influence of extracellular adenosine on melanoma progression with emphasis on the role of CD73.

I have generated a cell line with a stable CD73 knock-down – B16F10 CD73 KD, by means of RNA interference. The in vivo analysis of tumor growth performed on C57BL/6J mice and B16F10 cell line showed inhibition of tumor growth in mice with CD73 knock-out – CD73 KO and after administration of CD73 KD cells, CD73 inhibitor – AOPCP or P1 receptors' (adenosine receptors) agonists: IB-MECA, CGS 21680 and CCPA (agonists of receptor: A3, A2A and A1, respectively). Analysis of tumor angiogenesis in above tumors revealed reduction in number of vessels only after AOPCP administration and reversion of this effect with simultaneous administration of IB-MECA. Neither expression nor enzymatic activity of CD73 affected tumor infiltration with CD8+ lymphocytes, however tumors after administration of AOPCP and tumors derived from CD73 KD cells characterized in reduced macrophage infiltration. Administration of IB-MECA or CGS 21680 reversed that effect. I also demonstrated inhibition of B16F10 melanoma metastasis in CD73 KO mice after administration of CD73 KD cells or AOPCP. Administration of P1 receptors' agonists didn't influence the number of metastates.

Results presented here demonstrate, that in murine model of B16F10 melanoma CD73 promotes in vivo tumor growth and that extracellular adenosine promotes tumor angiogenesis. Though, in the model investigated, inhibition of angiogenesis is not the sole reason for tumor growth inhibition. Additionally, CD73 promotes B16F10 melanoma metastasis. The biological effects of chemical inhibition of CD73 and its knock-down on cancer cells differ in various aspects, which suggest additional, non-enzymatic functions of CD73 in tumor progression.

Czerniak to złośliwy nowotwór skóry, błony śluzowej oraz błony naczyniowej gałki ocznej, który wywodzi się z melanocytów i charakteryzuje się wysoką śmiertelnością. CD73 jest enzymem produkującym zewnątrzkomórkową adenozynę. Ze względu na swój udział w stymulacji angiogenezy nowotworowej, przerzutowaniu i regulacji odpowiedzi układu immunologicznego na nowotwór, może być nowym potencjalnym celem terapeutycznym.