Disruption of the CD39 immune checkpoint pathway increases the efficacy of various anticancer therapies in syngeneic mouse tumor models

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Abstract
The CD39–CD73–adenosine pathway is an emerging regulator of the immune antitumor response. CD39 is expressed within tumors and the tumor microenvironment by several cell populations including immune and cancer cells. In tumor tissues, the pathway leads to the accumulation of immunosuppressive adenosine with decreased levels of immunostimulating purine metabolites. We reported previously that CD39 blockade increased T cell and NK cell-mediated cytotoxic activity in vitro and in vivo. During the meeting, the development of the first human CD39-blocking antibody (5). Augier et al., Preclinical development of a humanized blocking antibody targeting the CD39 immune checkpoint for cancer immunotherapy. Here we demonstrated that this pathway is involved in tumor-induced resistance in various cancer therapies in syngeneic mouse melanomas, colon cancer and fibrosarcoma models. We used therapy-resistant mouse models or ineffective treatment regimens in the CD39 knockout mice to assess the capacity of CD39 to affect the response to chemotherapeutics, tumor associated antigens (TAA)-targeting antibodies and immunomodulators such as anti-PO1 antibodies. We achieved increased response rates, increased response duration and some complete and long lasting tumor regressions in the CD39 deficient context. These preclinical proof-of-concept studies highlight the role of the CD39 immune-checkpoint pathway in limiting the efficacy of various anticancer therapies in syngeneic mouse models and thereby support the potential clinical value of the humanized CD39 neutralizing antibody under development.

Methods summary

CD39 ecto-ATPase is functionally expressed in tumor microenvironment

TLRs from mouse tumors co-express CD39 and PD-1

Conclusions & Perspectives

We demonstrated here that CD39 is functionally expressed by immune cells from the tumor microenvironment in 3 different syngeneic tumor mouse models. We further showed that a high percentage of tumor infiltrating regulatory and effector lymphocytes co-express CD39 and PD-1, a particular phenotype not seen in spleen and lymph nodes from the same animals.

Using both PD-1 sensitive (MC38) and resistant (MC3U5) tumor models we demonstrated that CD39 deficiency sensitizes to anti-PD-1 treatment. We further demonstrated that the antitumor efficacy of CD39 disruption is improved when combined with an immunogenic chemotherapy, leading to complete tumor regression and specific anti-tumor immunity. In animals presenting PD-1 resistant tumors, combination of immunogenic chemotherapy, and PD-1 antibody and CD39 disruption led to complete and durable responses in most animals.

These results strongly support the development of our humanized CD39 specific blocking antibodies for cancer immunotherapy (Augier et al, AACR 2016 #2223).