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The role of tumor expression of CD200 in tumor formation, metastasis and susceptibility to T lymphocyte adoptive transfer therapy

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CD200 is a cell surface glycoprotein that has been implicated in a variety of human cancer cells and has been thought to play a pro-tumor role. However, in our recent study we have revealed that CD200 on cancer cells inhibits tumor formation and metastasis through inhibition of myeloid cells.

Myeloid cells are pivotal in tumor initiation, tumor mass formation, tumor progression and metastasis.[1] In the tumor initiation and formation stage, myeloid cells produce an array of factors that promote tumor establishment. During the tumor progression and metastasis stages, myeloid cells provide support for developing tissues through their matrix remodeling capacities, synthesis of growth and angiogenesis factors and capacities in suppressing antitumor immunity. Genetic ablation, depletion of myeloid cells or inhibition of myeloid cell functions have been shown to be effective in inhibiting tumor establishment and tumor progression. Increased number of myeloid cells has been shown to be associated with shortened survival of cancer patients. Thus, tumor associated myeloid cells (TAMC) have been proposed as targets for therapeutic intervention.[2]

CD200 (also known as OX-2) is a member of the Ig super family (IgSF) of proteins. It contains two extracellular immunoglobulin domains and a small intracellular domain with no known signaling motif. CD200R, the cognate ligand for CD200, is also an IgSF protein whose expression is mainly restricted to the myeloid lineage of cells.[3] CD200-CD200R interaction is involved in limiting the cellular functions of myeloid lineage of cells, as CD200 deficient mice were found to have hyper activation of macrophages and enhanced inflammation in autoimmune disease models.[4]

Since TAMCs are the major lineages of cells expressing CD200R in the tumor microenvironment[5] and expression of CD200 has been found in multiple types of cancer including melanoma, we hypothesized that tumor expression of CD200 inhibits the functions of TAMCs and thereby affects tumor formation, metastasis and susceptibility to T-cell therapy. In a recent study,[6] we have tested this hypothesis and we have made the following three observations.

First, we have found that expression of CD200 on melanoma cells dramatically inhibits tumor foci formation in the lungs of both C57BL/6 and Rag1$^{-/-}$ C57BL/6 mice. Lung tumor formation and metastasis appear to be mediated by CD200R^{+}Gr-1^{+} lung myeloid cells, as depletion of Gr-1^{+} myeloid cells using anti-Gr1 mAb abrogated lung tumor formation and metastasis of B16 melanoma. In vitro co-culture experiments revealed that CD200-positive tumor cells but not CD200-negative tumor cells strongly suppress production of cytokines by myeloid cells. Thus, our data establish that tumor expression of CD200 inhibits tumor formation and metastasis via inhibiting CD200R^{+} myeloid cells. CD200 on cancer cells has previously been thought to play a pro-tumor role. In an animal study, CD200 expression was found to be positively correlated with the metastatic capacity of squamous cell carcinoma.[7] However, it remains unclear if the induction of CD200 on tumor cells is responsible for tumor metastasis in that study. CD200 mRNA expression in myeloma cells has also been shown to be associated with decreased survival of patients.[8] However, this result was challenged recently by another report, showing that loss of CD200 protein expression, but not expression of CD200 on myeloma cells correlates with clinically more aggressive disease.[9] Thus, more studies are required for a solid conclusion in correlation studies.

Second, we have found that triggering CD200R using an agonistic monoclonal antibody (OX110) dramatically reduced CD200-negative melanoma tumor formation in the lungs. Anti-CD200R mAb treatment significantly diminished production of cytokines by CD11b^{+} myeloid cells,[6] suggesting that mAb OX110 can inhibit the functions of myeloid cells via engaging CD200R.

Third, as we previously demonstrated,[5] we found that adoptive transfer of tumor antigen-specific T cells

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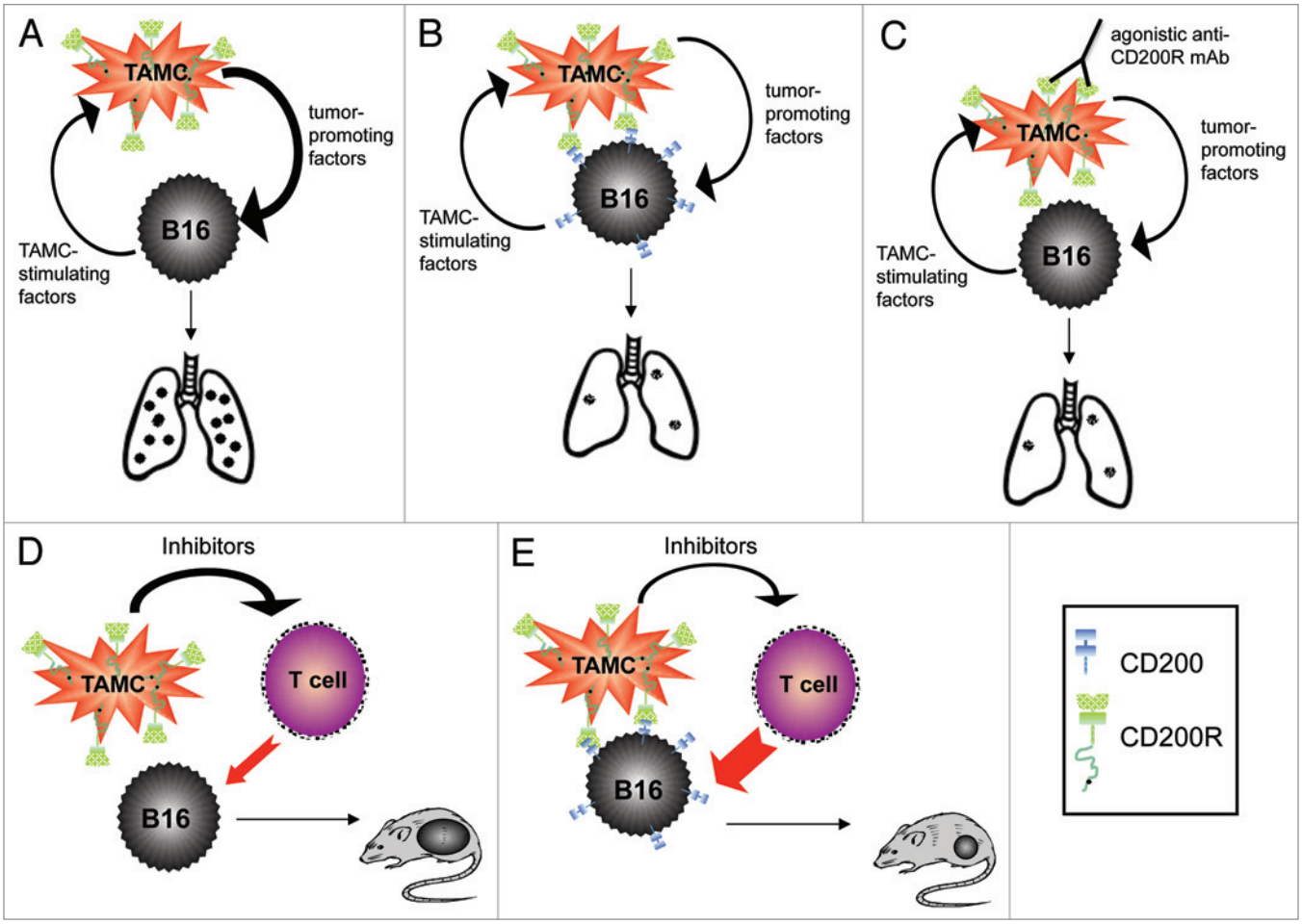

Figure 1. The impacts of tumor expression of CD200 on melanoma lung metastasis and susceptibility to T cell therapy. Melanoma lung tumor formation depicted in the absence (**A**) and presence (**B**) of CD200 expression on tumor cells. An agonistic antibody to CD200R inhibits melanoma lung tumor formation and metastasis (**C**). T cell therapy of mice with established tumors whose tumor cells are negative for CD200 (**D**) or positive for CD200 (**E**).

(both CD4 and CD8) significantly promots survival of mice with CD200-positive melanoma tumors over CD200-negative tumors. CD200-expressing melanoma cells were shown to down-regulate Th1 cytokine production when co-cultured with allogenic leukocytes.[10] It therefore was predicted that CD200-CD200R interaction induces suppression of anti-tumor T-cell responses. However, we have found that CTL barely express CD200R and tumor expression of CD200 does not inhibit effector functions of CTL.[5] Thus, our data suggest that tumor expression of CD200 is likely affecting T-cell effector functions via inhibiting TAMCs.

Taken together, our findings can be summarized in a model presented in **Figure 1**. Tumor cells recruit and interact with CD200R-positive myeloid cells. In the absence of CD200 inhibitory signal, TAMCs produce an array of cytokines, growth factors, enzymes and effector molecules such as reactive nitrogen/oxygen species that stimulate tumor formation and metastasis (**Fig. 1A**). In the presence of CD200 inhibitory signal, TAMCs have reduced production of those tumor promoting factors, which leads to reduced tumor formation and metastasis (**Fig. 1B**). Using a triggering antibody to CD200R could achieve similar results as CD200-expression on tumor cells (**Fig. 1C**). Finally, in an established CD200-negative tumor, production of high amounts of M2 cytokines and inhibitors by TAMCs lead to a very suppressive tumor microenvironment, which inhibits T-cell effector function and tumor rejection (**Fig. 1D**). In the presence of CD200 signal delivered by tumor cells, reduced production of immune inhibitors by TAMCs lead to enhanced T-cell effector function and tumor rejection (**Fig. 1E**).

Given the important roles of CD200-CD200R interaction in regulating tumor associated myeloid cells and inhibiting tumor formation and metastasis, targeting CD200-CD200R interaction should provide an option for the immunotherapy of human cancer. Because of the restricted expression of CD200R to myeloid cells and the importance of these cells in essentially all tumor types, targeting CD200R should be an ideal option. Our successful treatment of CD200-negative tumors using a triggering anti-CD200R mAb proves that this approach is feasible.

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