

B7 family member programmed-death-1-ligand 2 with

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What is known about programmed-death-1 ligand 2?

Peter Steinberger: Programmed-death-1-ligand 2 (PD-L2/B7-DC) is a member of the B7 family of molecules. In contrast to other so-called B7 homologs like ICOSL, PD-L1/B7-H1 or B7-H3 that are also expressed in peripheral tissues,

PD-L2 expression is restricted mainly to dendritic cells and activated macrophages (1). Like PD-L1 it interacts with programmed-death-receptor 1 (PD-1), an inhibitory receptor that is induced on T cells upon activation.

Why are your findings on human T cells different from studies on mouse T cells?

Peter Steinberger: Our findings on PD-L2 differ from some studies on mouse T cells but they are in agreement with data from other investigators that found murine PD-L2 to inhibit T cell activation (2-4). These studies are in line with the function of PD-1, which is well established to act as a negative regulator of T cell activation. However there are a number of studies that describe a costimulatory function for PD-L2 on mouse T cells and thus the existence of an alternative so far unidentified PD-L2 receptor has been proposed (1,5-8).

In contrast all studies on human T cells find PD-L2 to be a negative regulator of T cell activation. Initial studies showed that inhibiting PD-L2 on DC or on activated PBMC resulted in enhanced T cell responses and that blocking PD-L2 on endothelial cells augments CD8⁺ T cell activation (9-11). Since these studies were done with a mAb to PD-L2 one could still argue that the antibody that was used in these studies blocks the inhibitory PD-L2/PD-1 pathway but leaves a putative costimulatory pathway involving PD-L2

unaffected. However recently the function of human PD-L2 has been analyzed directly by using PD-L2-Ig fusion proteins in conjunction with anti-CD3 antibodies (12). This study again reported only inhibitory functions for human PD-L2 on T cell proliferation, cytokine production and interestingly also integrin-mediated adhesion.

We have in our study investigated the function of PD-L2 in T cell activation using a novel system of T cell stimulator cells that express a membrane-bound anti-CD3 antibody that triggers the T cell receptor complex thereby conveying "Signal 1" to human T cells (13). By expressing PD-L2 on these stimulator cells the contribution of this B7 family member to T cell activation processes was studied. In line with previous work we found PD-L2 to inhibit proliferation, up-regulation of activation markers and cytokine production of human T cells by interacting with PD-1. In our study we specifically addressed a putative costimulatory role of this molecule by analysing PD-L2 under experimental conditions where it was described

to act costimulatory in murine systems. Importantly we found human PD-L2 not to act costimulatory in any of these settings. Furthermore we have for the first time analyzed the interaction of PD-L2-Ig fusion proteins with human T cells. In line with our functional data we found no evidence for non-PD-1 receptors as PD-L2 interaction with human T cells was completely

blocked by PD-1 antibodies (13). Taken together all current data on the role of PD-L2 on human T cells clearly differ from several studies by independent investigators that report costimulatory functions for mouse PD-L2. In my opinion this accentuates the importance of studies on human cells to get an insight on the function of the newly identified B7 family members in humans.

Do you believe that PD-L2 is a candidate molecule for immunotherapeutic approaches?

Peter Steinberger: I believe that PD-L2 has considerable therapeutic potential. For instance one could envision blocking PD-L2 on APC/DC as a strategy to enhance anti-tumour immunity in humans. On the other hand therapeutic approaches aimed to express inhibitory molecules at sites of pathological immune responses might be a mean to ameliorate autoimmune conditions. I think that PD-L2 might be a good candidate molecule for such strategies. As pointed out above the receptor PD-1 can receive inhibitory signals by interacting with PD-L1 or PD-L2. Thus

fusion proteins representing PD-1 or antagonistic PD-1 antibodies might be efficient tools to boost immune response by blocking the interaction of both PD-Ls with PD-1. However like for PD-L2 also for PD-L1 costimulatory functions have been reported and thus the existence of costimulatory PD-L1 receptors was proposed (8,14). Resolving the debate of costimulatory PD-Ligand receptors for instance by identifying such molecules in mice or humans is imperative and would also aid attempts to therapeutically exploit the inhibitory PD-L/PD-1 pathway.

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