PD-L1

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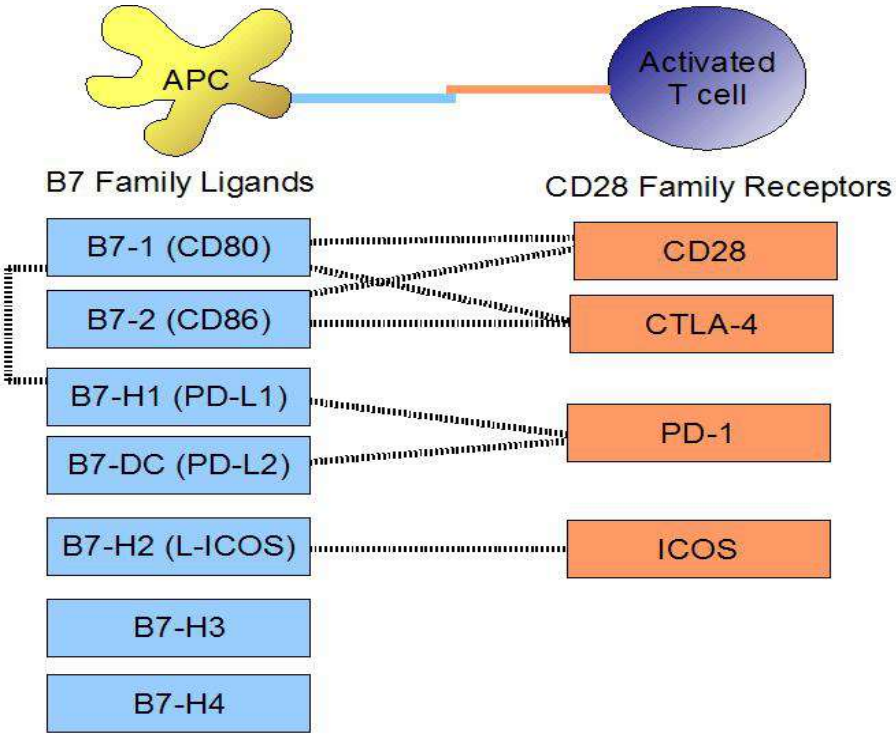
Programmed death-ligand 1 (PD-L1) also known as **cluster of differentiation** 274 (CD274) or **B7 homolog 1** (B7-H1) is a protein that in humans is encoded by the *CD274* gene.[5]

Programmed death-ligand 1 (PD-L1) is a 40kDa type 1 transmembrane protein that has been speculated to play a major role in suppressing the immune system during particular events such as pregnancy, tissue allografts, autoimmune disease and other disease states such as hepatitis. Normally the immune system reacts to foreign antigens that are associated with exogenous or endogenous Danger signals, which triggers a proliferation of antigen-specific CD8+ T cells and/or CD4+ helper cells. The binding of PD-L1 to PD-1 or B7.1 transmits an inhibitory signal that reduces the proliferation of these T cells and can also induce apoptosis, which is further mediated by a lower regulation of the gene Bcl-2.[6]

History

PD-L1 was characterized at the Mayo Clinic as an immune regulatory molecule, B7-H1. Later this molecule was renamed as PD-L1 because it was identified as a ligand of PD-1[7] Several human cancer cells expressed high levels of B7-H1, and blockade of B7-H1 reduced the growth of tumors in the presence of immune cells. At that time it was concluded that B7-H1 helps tumor cells evade anti-tumor immunity.[8]

Binding



PD-L1 binds to its receptor, PD-1, found on activated T cells, B cells, and myeloid cells, to modulate activation or inhibition. The affinity between PD-L1 and PD-1, as defined by the dissociation constant K_d, is 770nM. Interestingly, PD-L1 also has an appreciable affinity for the costimulatory molecule CD80 (B7-1), but not CD86 (B7-2).[9] CD80's affinity for PD-L1, 1.4μM, is intermediate between its affinities for CD28 and CTLA-4 (4.0μM and 400nM, respectively). The related molecule PD-L2 has no such affinity for CD80 or CD86, but shares PD-1 as a receptor (with a stronger K_d of 140nM). Said et al. showed that PD-1, up-regulated on activated CD4 T-cells, can bind to PD-L1 expressed on monocytes and induces IL-10 production by the latter.[10]

Signaling

Engagement of PD-L1 with its receptor PD-1 on T cells delivers a signal that inhibits TCR-mediated activation of IL-2 production and T cell proliferation. The mechanism involves inhibition of ZAP70 phosphorylation and its association with CD3ζ.[11] PD-1 signaling attenuates PKC-θ activation loop phosphorylation (resulting from TCR signaling), necessary for the activation of transcription factors NF-κB and AP-1, and for production of IL-2.

PD-L1 binding to PD-1 also contributes to ligand-induced TCR down-modulation during antigen presentation to naive T cells, by inducing the up-regulation of the E3 ubiquitin ligase CBL-b.[12]

Regulation

By interferons

Upon IFN-γ stimulation, PD-L1 is expressed on T cells, NK cells, macrophages, myeloid DCs, B cells, epithelial cells, and vascular endothelial cells.[13] The PD-L1 gene promoter region has a response element to IRF-1, the interferon regulatory factor.[14] Type I interferons can also upregulate PD-L1 on murine hepatocytes, monocytes, DCs, and tumor cells.[15]

On macrophages

PD-L1 is notably expressed on macrophages. In the mouse, it has been shown that classically activated macrophages (induced by type I helper T cells or a combination of LPS and interferon-gamma) greatly upregulate PD-L1.[16] Alternatively, macrophages activated by IL-4 (alternative macrophages), *slightly* upregulate PD-L1, while greatly upregulating PD-L2. It has been shown by STAT1-deficient knock-out mice that STAT1 is mostly responsible for upregulation of PD-L1 on macrophages by LPS or interferon-gamma, but is not at all responsible for its constitutive expression before activation in these mice.

Role of microRNAs

Resting human cholangiocytes express PD-L1 mRNA, but not the protein, due to translational suppression by microRNA miR-513.[17] Upon treatment with interferon-gamma, miR-513 was down-regulated, thereby lifting suppression of PD-L1 protein. In this way, interferon-gamma can induce PD-L1 protein expression by inhibiting gene-mediated suppression of mRNA translation.

Epigenetic regulation

PD-L1 promoter DNA methylation may predict survival in some cancers after surgery.[18]

Clinical significance

Cancer

It appears that upregulation of PD-L1 may allow cancers to evade the host immune system. An analysis of 196 tumor specimens from patients with renal cell carcinoma found that high tumor expression of PD-L1 was associated with increased tumor aggressiveness and a 4.5-fold increased risk of death.[19] Many PD-L1 inhibitors are in development as immuno-oncology therapies and are showing good results in clinical trials.[20] Clinically available examples include Durvalumab, atezolizumab and avelumab.[21] In normal tissue, feedback between transcription factors like STAT3 and NF-κB restricts the immune response to protect host tissue and limit inflammation. In cancer, loss of feedback restriction between transcription factors can lead to increased local PD-L1 expression, which could limit the effectiveness of systemic treatment with agents targeting PD-L1. [22]

Listeria monocytogenes

In a mouse model of intracellular infection, *L. monocytogenes* induced PD-L1 protein expression in T cells, NK cells, and macrophages. PD-L1 blockade (using blocking antibodies) resulted in increased mortality for infected mice. Blockade reduced TNFα and nitric oxide production by macrophages, reduced granzyme B production by NK cells, and decreased proliferation of *L. monocytogenes* antigen-specific CD8 T cells (but not CD4 T cells).[23] This evidence suggests that PD-L1 acts as a positive costimulatory molecule in intracellular infection.

Autoimmunity

The PD-1/PD-L1 interaction is implicated in autoimmunity from several lines of evidence. NOD mice, an animal model for autoimmunity that exhibit a susceptibility to spontaneous development of type I diabetes and other autoimmune diseases, have been shown to develop precipitated onset of diabetes from blockade of PD-1 or PD-L1 (but not PD-L2).[24]

In humans, PD-L1 was found to have altered expression in pediatric patients with Systemic lupus erythematosus (SLE). Studying isolated PBMC from healthy children, immature myeloid dendritic cells and monocytes expressed little PD-L1 at initial isolation, but spontaneously up-regulated PD-L1 by 24 hours. In contrast, both mDC and monocytes from patients with active SLE failed to upregulate PD-L1 over a 5-day time course, expressing this protein only during disease remissions.[25] This may be one mechanism whereby peripheral tolerance is lost in SLE.