Programmed cell death 1

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Programmed cell death protein 1, also known as **PD-1** and **CD279** (cluster of differentiation 279), is a protein that in humans is encoded by the *PDCD1* gene.[1][2] PD-1 is a cell surface receptor that belongs to the immunoglobulin superfamily and is expressed on T cells and pro-B cells.[2] PD-1 binds two ligands, PD-L1 and PD-L2.

PD-1, functioning as an immune checkpoint, plays an important role in down regulating the immune system by preventing the activation of T-cells, which in turn reduces autoimmunity and promotes self-tolerance. The inhibitory effect of PD-1 is accomplished through a dual mechanism of promoting apoptosis (programmed cell death) in antigen specific T-cells in lymph nodes while simultaneously reducing apoptosis in regulatory T cells (suppressor T cells).[3][4]

A new class of drugs that block PD-1, the **PD-1 inhibitors**, activate the immune system to attack tumors and are therefore used with varying success to treat some types of cancer.[5]

Structure

Programmed death 1 is a type I membrane protein of 268 amino acids. PD-1 is a member of the extended CD28/CTLA-4 family of T cell regulators.[6] The protein's structure includes an extracellular IgV domain followed by a transmembrane region and an intracellular tail. The intracellular tail contains two phosphorylation sites located in an immunoreceptor tyrosine-based inhibitory motif and an immunoreceptor tyrosine-based switch motif, which suggests that PD-1 negatively regulates TCR signals.[6][7] This is consistent with binding of SHP-1 and SHP-2 phosphatases to the cytoplasmic tail of PD-1 upon ligand binding. In addition, PD-1 ligation up-regulates E3-ubiquitin ligases CBL-b and c-CBL that trigger T cell receptor down-modulation.[8] PD-1 is expressed on the surface of activated T cells, B cells, and macrophages,[9] suggesting that compared to CTLA-4, PD-1 more broadly negatively regulates immune responses.

Ligands

PD-1 has two ligands, PD-L1 and PD-L2, which are members of the B7 family.[10][11] PD-L1 protein is upregulated on macrophages and dendritic cells (DC) in response to LPS and GM-CSF treatment, and on T cells and B cells upon TCR and B cell receptor signaling, whereas in resting mice, PD-L1 mRNA can be detected in the heart, lung, thymus, spleen, and kidney.[10][12] PD-L1 is expressed on almost all murine tumor cell lines, including PA1 myeloma, P815 mastocytoma, and B16 melanoma upon treatment with IFN-γ.[13][14] PD-L2 expression is more restricted and is expressed mainly by DCs and a few tumor lines.[11]

Function

Several lines of evidence suggest that PD-1 and its ligands negatively regulate immune responses. PD-1 knockout mice have been shown to develop lupus-like glomerulonephritis and dilated cardiomyopathy on the C57BL/6 and BALB/c backgrounds, respectively.[15][16] In vitro, treatment of anti-CD3 stimulated T cells with PD-L1-Ig results in reduced T cell proliferation and IFN-γ secretion.[10] Reduced T cell proliferation correlated with attenuated IL-2 secretion, which can be rescued by addition of cross-linking anti-CD28 antibodies or exogenous IL-2.[17]

Together, these data suggest that PD-1 negatively regulates T cell responses. Experiments using PD-L1 transfected DCs and PD-1 expressing transgenic (Tg) $CD4^+$ and $CD8^+$ T cells suggest that $CD8^+$ T cells are more susceptible to inhibition by PD-L1, although this could be dependent on the strength of TCR signaling. Consistent with a role in negatively regulating $CD8^+$ T cell responses, using an LCMV model of chronic infection, Rafi Ahmed's group showed that the PD-1-PD-L1 interaction inhibits activation, expansion and acquisition of effector functions of virus specific $CD8^+$ T cells, which can be reversed by blocking the PD-1-PD-L1 interaction.[18]

As CTLA-4 negatively regulates anti-tumor immune responses, the closely related molecule PD-1 has been independently explored as a target for immunotherapy. The 2C TCR recognizes the peptide SIYRYYGL in the context of H 2kb. 2C CD8 T cells incubated with IFN-γ treated B16 targets expressing SIYRYYGL peptide poorly lyse their targets and secrete low levels of IL-2.[14] However, PD-1 knockout 2C T cells have heightened cytolytic capacity and IL-2 secretion, suggesting that PD-1 negatively regulates anti-tumor CD8 T cell responses. Similarly, P815 mastocytoma, which does not express PD-L1 unless treated with IFN-γ, can be transduced to express PD-L1, resulting in inhibition of in vitro CD8-mediated cytotoxicity and enhanced in vivo tumor growth. In vitro cytotoxicity and in vivo inhibition of growth can be restored by anti-PD-L1 antibodies or by genetic ablation of PD-1[13][14] Together, these data suggest that expression of PD-L1 on tumor cells inhibits anti-tumor activity through engagement of PD-1 on effector T cells. Expression of PD-L1 on tumors is correlated with reduced survival in esophageal, pancreatic and other types of cancers, highlighting this pathway as a target for immunotherapy.[19] Said et al. showed that triggering PD-1, expressed on monocytes and up-regulated upon monocytes activation, by its ligand PD-L1 induces IL-10 production which inhibits CD4 T-cell function.[20]

Clinical significance

In mice, expression of this gene is induced in the thymus when anti-CD3 antibodies are injected and large numbers of thymocytes undergo apoptosis. Mice deficient for this gene bred on a BALB/c background developed dilated cardiomyopathy and died from congestive heart failure. These studies suggest that this gene product may also be important in T cell function and contribute to the prevention of autoimmune diseases.[2]

Cancer

Monoclonal antibodies targeting PD-1 that boost the immune system are being developed for the treatment of cancer.[21] Many tumor cells express PD-L1, an immunosuppressive PD-1 ligand; inhibition of the interaction between PD-1 and PD-L1 can enhance T-cell responses *in vitro* and mediate preclinical antitumor activity. This is known as immune checkpoint blockade.

One such anti-PD-1 antibody drug, nivolumab, (Opdivo - Bristol Myers Squibb), produced complete or partial responses in non-small-cell lung cancer, melanoma, and renal-cell cancer, in a clinical trial with a total of 296 patients.[22] Colon and pancreatic cancer did not have a response.

Nivolumab (Opdivo, Bristol-Myers Squibb), which also targets PD-1 receptors, was approved in Japan in July 2014 and by the US FDA in December 2014 to treat metastatic melanoma.

Pembrolizumab (Keytruda, MK-3475, Merck), which also targets PD-1 receptors, was approved by the FDA in Sept 2014 to treat metastatic melanoma. Pembrolizumab has been made accessible to advanced melanoma patients in the UK via UK Early Access to Medicines Scheme (EAMS) in March 2015. It is being used in clinical trials in the US for lung cancer, lymphoma, and mesothelioma. It has had measured success, with little side effects.It is up to the manufacturer of the drug to submit application to the FDA for approval for use in these diseases. On October 2, 2015 Pembrolizumab was approved by FDA for advanced (metastatic) non-small cell lung cancer (NSCLC) patients whose disease has progressed after other treatments.[23] Other drugs in early stage development targeting PD-1 receptors (aka checkpoint inhibitors): Pidilizumab (CT-011, Cure Tech), BMS 936559 (Bristol Myers Squibb), and MPDL328OA (Roche)

HIV

Drugs targeting PD-1 may augment immune responses and/or facilitate HIV eradication.[24]