- An antibody that binds to a ligand or to a receptor can be blocking. Alternatively, the antibody can be activating and can result in transmission of a signal into the cell. Whether an antibody is blocking or inhibiting may depend on the exact conformation and contact points between the antibody binds to the ligand (or binds to the receptor).
- *Nivolumab* is an anti-PD-1 antibody. Nivolumab has been tested for treating various cancers (66,67). Novilumab was FDA-approved in March 2015 for the indication of NSCLC, and in Dec. 2015 for melanoma.
- *Pembrolizumab* is an anti-PD-1 antibody that was FDA-approved in September 2014, for melanoma.
- *Ipilimumab* is an anti-CTLA-4 antibody that was FDA-approved in March 2011 for melanoma.
- *BMS-9365559* is an anti-PD-L1 antibody that has been used in clinical trials on subjects with NSCLC, melanoma, colorectal cancer, renal-cell cancer, ovarian cancer, pancreatic cancer, gastric cancer, and breast cancer (68).

f. Priming

CTLA-4 is not expressed on the surface of T cells that are resting. CTLA-4 appears on the surface of T cells only with T-cell activation (69). DCs activate T cells by way of two signals:

- *First signal*. The first signal is delivered by the DC's MHC/antigen complex to TCR. TCR resides on the surface of the T cell.
- *Second signal*. The second signal is delivered by the DC's B7-1 and B7-2 to the T cell's CD28.

Dendritic cells present antigens to T cells in a step called priming. However, priming without more is not enough to result in an effective immune response. What is also needed is a co-stimulatory signal, originating from B7-1 or B7-2, where these signals are transmitted to CD28 of the T cell. In other words, what is needed is priming and also a co-stimulatory signal.

g. B7/CD28 Signaling and B7/CTLA-4 Signaling

B7 proteins have a much higher affinity for CTLA-4 than for CD28, and thus materialization of CTLA-4 on the surface of the T cells persuades B7 to leave CD28 and instead to bind to CTLA-4. This dissipates the B7/CD28 signaling (70).

The time element in T-cell activation is revealed by a scenario that involves CD28, B7-1, and B7-2. When a DC contacts a T cell, initially it is the case that the DC's B7-1 and B7-2 engage CD28 on naive T cells. Subsequently, CTLA-4 is expressed on the activated T cell, with the consequence that B7-1 and B7-2 are distracted from their binding to CD28, and instead bind to CTLA-4, thus dampening and attenuating the activity of the activated T cell (71).

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