the "scurfy mouse." Scurfy mouse has a genetic defect in the *FOXP3* gene. These mice lack Tregs, and their T cells proliferate indefinitely, leading to massive inflammation, overwhelming autoimmunity, and death (47).

But the Tregs that are associated with tumors only help the tumor evade immune attack. Tregs exert their immunosuppressive influences by killing $CD8^+$ T cells by way of the death receptor (CD95) and by secreting immunosuppressive cytokines, IL-10 and TGF-beta (48,49). Regarding TGF-beta, this cytokine is expressed by a wide variety of tumors. TGF-beta occurs at high levels in the plasma of cancer patients. The immunosuppressive effects of TGF-beta take the form of inhibiting cytotoxic lymphocytes, that is, inhibiting their expression of granzyme and of IFN-gamma (50).

f. Immune Evasion With PD-1 Signaling

PD-L1 (ligand) is a membrane-bound protein that is expressed by various tumor cells. PD-L1 is not just expressed by tumor cells, but it may also be expressed by the lymphocytes that infiltrate tumors (51).

PD-1 is the corresponding receptor. PD-1 is expressed by most kinds of lymphocytes that may infiltrate into the tumor. PD-1 is expressed by T cells, B cells, monocytes, natural killer T cells (NK cells), and macrophages (52,53).

Where the tumor cell's PD-L1 engages PD-1 of a T cell, the result is that the tumor can inhibit attack by the T cell (54). In the words of Garon et al. (55), "[o]ne hallmark of cancer is immune evasion, in which the immune system does not mount an effective antitumor response … PD-1 is a negative costimulatory receptor expressed … on the surface of activated T cells. The binding of PD-1 to … PD-L1 … can inhibit a cytotoxic T-cell response. Tumors can co-opt this pathway to escape T-cell-induced antitumor activity."

This binding of PD-L1 to PD-1, which is a part of immune evasion, is vividly illustrated by the fact that blocking antibodies against either the ligand (PD-L1) or the receptor (PD-1) can dramatically increase survival against cancer. In other words, the antibody prevents the tumor from engaging in this tactic of immune evasion.

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