many tumors. In detail, PD-L1 is not expressed in normal epithelial tissues, but it is expressed by cancer cells, including in breast cancer, renal-cell cancer, pancreatic cancer, ovarian cancer, gastric cancer, and hepatocellular cancer (81).

Mechanisms by which cancer cells evade the immune system, where the cancer cells take advantage of PD-1–PD-L1 interactions, are provided by Brahmer et al. (82). In a study of one type of *breast cancer*, researchers found that the breast cancer cells increased their expression of PL-L1, where the result was decreased proliferation of the T cells and increased death of the T cells (83). Histological studies of *melanoma* tumors revealed that PD-L1 can be either nondetectable on the melanoma cells, or expressed diffusely on the surface of melanoma cells, or alternatively, highly localized in "discrete geographic foci" with "highly co-localized" T cells that have infiltrated the melanoma tumor (84). PD-L1 is expressed in 40–50% of melanomas and has limited expression otherwise in most visceral organs with the exception of respiratory epithelium and placental tissue (85).

II. IMMUNE EVASION

Immune evasion by cancer cells involves a number of mechanisms, including T-cell exhaustion, immunosuppressive cytokines that "cool down" the immune system, such as the cytokine interleukin-10 (IL-10). Accounts of IL-10 in immune evasion have been reviewed (86,87). Immune evasion also can involve Tregs (88). The term, "tumor microenvironment" is used in studies of tumors, of the immune cells that infiltrate tumors, and of the immunosuppressive cytokines that are released by the cancer cells.

PD-L1/PD-1-mediated T cell exhaustion is shown in Figure 27.3. Both $CD8^+$ T cells and $CD4^+$ T cells are susceptible to immune exhaustion (89). When CTLA-4 is activated, CTLA-4 can enhance the immunosuppressive functions of Tregs (90).

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