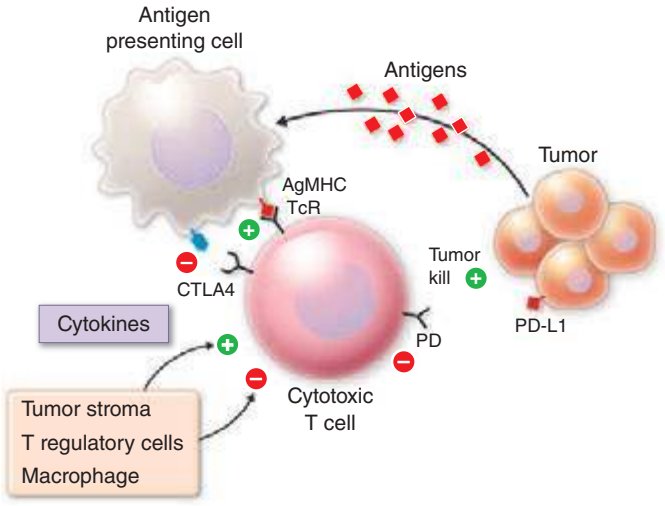


**FIGURE 103e-5 Tumors possess a microenvironment (tumor stroma) with immune cells including both helper T cells, suppressor T cells (both "regulatory" of other immune cell function), macrophages, and cytotoxic T cells.** Cytokines found in the stroma and deriving from macrophawsges and regulatory T cells modulate the activities of cytotoxic T cells, which have the potential to kill tumor cells. Antigens released by tumor cells are taken up by Antigen Presenting Cells (APCs), also in the stroma. Antigens are processed by the APCs to peptides presented by the Major Histocompatibility Complex to T-cell antigen receptors, thus providing an (+) activation signal for the cytotoxic tumor cells to kill tumor cells bearing that antigen. Negative (–) signals inhibiting cytoxic T cell action include the CTLA4 receptor (on T cells), interacting with the B7 family of negative regulatory signals from APCs, and the PD receptor (on T cells), interacting with the PD-L1 (–) signal coming from tumor cells expressing the PD-1 ligand (PD-l1). As both CTLA4 and PD1 signals attenuate the anti-tumor T cell response, strategies which inhibit CTLA4 and PD1 function are a means of stimulating cytotoxic T cell activity to kill tumor cells. Cytokines from other immune cells and macrophages can provide both (+) and (–) signals for T cell action, and are under investigation as novel immunoregulatory therapeutics.

Already approved for clinical use in melanoma is ipilimumab, an antibody directed against the anti-CTLA4 (cytotoxic T lymphocyte antigen 4), which is expressed on T cells (not tumor cells), responds to signals from antigen-presenting cells (Fig. 103e-5), and also downregulates the intensity of the T cell proliferative response to antigens derived from tumor cells. Indeed, manipulation of the CTLA4 axis was the first demonstration that purely immunoregulatory antibody strategies directed at T cell physiology could be safe and effective in the treatment of cancer, although it acts at a very early stage in T cell activation and can be considered somewhat nonspecific in its basis for T cell stimulation. Pembrolizumab, an anti-PD ligand blocking agent was also approved for melanoma, with a similar spectrum of potential adverse events, but acting in the tumor microenvironment. Indeed, prominent activation of autoimmune hepatic, endocrine, cutaneous, neurologic, and gastrointestinal responses is a basis for adverse events with the use of ipilimumab; the emergent use of glucocorticoids may be required to attenuate severe toxicities, which unfortunately can cause potential attenuation of antitumor effect. Importantly for the general internist, these events may occur late after exposure to ipilimumab while the patient may otherwise be enjoying sustained control of tumor growth owing to the beneficial actions of ipilimumab.

Another class of immunoregulatory antibody is the "bispecific" antibody blinatumomab, which was constructed to have an anti-CD19 antigen combining site as one valency of an antibody with anti-CD3 binding site as the other valency. This antibody thus can bring T cells (with its anti-CD3 activity) close to B cells bearing the CD19 determinant. Blinatumomab is active in B cell neoplasms such as acute lymphocytic leukemia, which may not have prominent expression of the CD20 targeted by rituximab.

***ANTIBODY CONJUGATES*** Conjugates of antibodies with drugs and isotopes have also been shown to be effective in the treatment of cancer and have the intent of increasing the therapeutic index of the drug or isotope by delivering the toxic "warhead" directly to the tumor cell or tumor microenvironment. Ado-trastuzumab is a conjugate of the HER2/neu-directed trastuzumab and a highly toxic microtubule targeted drug (emtansine), which by itself is too toxic for human use; the antibody-drug conjugate shows valuable activity in patients with breast cancer who have developed resistance to the "naked" antibody. Brentuximab vedotin is an anti-CD30 antibody drug conjugate with a distinct microtubule poison with activity in neoplasms such as Hodgkin's lymphoma where the tumor cells frequently express CD30. Radioconjugates targeting CD20 on lymphomas have been approved for use (ibritumomab tiuxetan [Zevalin], using yttrium-90 or $^{131}$I-tositumomab). Toxicity concerns have limited their use.

**Cytokines** There are >70 separate proteins and glycoproteins with biologic effects in humans: interferon (IFN) α, β, and γ; interleukin (IL) 1 through 29 (so far); the tumor necrosis factor (TNF) family (including lymphotoxin, TNF-related apoptosis-inducing ligand [TRAIL], CD40 ligand, and others); and the chemokine family. Only a fraction of these has been tested against cancer; only IFN-α and IL-2 are in routine clinical use.

About 20 different genes encode IFN-α, and their biologic effects are indistinguishable. IFN induces the expression of many genes, inhibits protein synthesis, and exerts a number of different effects on diverse cellular processes. The two recombinant forms that are commercially available are IFN-α2a and -α2b. Interferon is not curative for any tumor but can induce partial responses in follicular lymphoma, hairy cell leukemia, CML, melanoma, and Kaposi's sarcoma. It has been used in the adjuvant setting in stage II melanoma, multiple myeloma, and follicular lymphoma, with uncertain effects on survival. It produces fever, fatigue, a flulike syndrome, malaise, myelosuppression, and depression and can induce clinically significant autoimmune disease. IFN-α is not generally the treatment of choice for any cancer.

IL-2 exerts its antitumor effects indirectly through augmentation of immune function. Its biologic activity is to promote the growth and activity of T cells and natural killer (NK) cells. High doses of IL-2 can produce tumor regression in certain patients with metastatic melanoma and renal cell cancer. About 2–5% of patients may experience complete remissions that are durable, unlike any other treatment for these tumors. IL-2 is associated with myriad clinical side effects, including intravascular volume depletion, capillary leak syndrome, adult respiratory distress syndrome, hypotension, fever, chills, skin rash, and impaired renal and liver function. Patients may require blood pressure support and intensive care to manage the toxicity. However, once the agent is stopped, most of the toxicities reverse completely within 3–6 days.

**Ligand Receptor–Directed Constructs** High-affinity receptors for cytokines have led to the design of cytokine-toxin recombinant fusion proteins, such as IL-2 expressed in frame with a fragment of diphtheria toxin. A commercially available construct has activity against certain T cell lymphomas. Likewise, the high-affinity folate receptor is the target for folate conjugated to chemotherapeutic agents. In both cases, the drug's utility derives from the internalization of the targeted receptor and cleavage of the active drug or toxin moiety.

## SYSTEMIC RADIATION THERAPY

Although total-body irradiation has a role in preparing a patient to received allogeneic stem cells, and antibodies as described above can specifically target radioisotopes, systemically administered isotopes of iodide salts have an important role in the treatment of thyroid neoplasms, owing to the selective upregulation of the iodide transporter in the tumor cell compartment. Likewise, isotopes of samarium and radium have been found useful in the palliation of symptoms from