Bevacizumab, an antibody that binds VEGF, appears to potentiate the effects of a number of different types of active chemotherapeutic regimens used to treat a variety of different tumor types including colon cancer, lung cancer, cervical cancer, and RCC.

Bevacizumab is administered IV every 2–3 weeks (its half-life is nearly 20 days) and is generally well tolerated. Hypertension is the most common side effect of inhibitors of VEGF (or its receptors), but can be treated with antihypertensive agents and rarely requires discontinuation of therapy. Rare but serious potential risks include arterial thromboembolic events, including stroke and myocardial infarction, and hemorrhage. Another serious complication is bowel perforation, which has been observed in 1–3% of patients (mainly those with colon and ovarian cancers). Inhibition of wound healing is also seen.

Several small-molecule inhibitors (SMIs) that target VEGFR tyrosine kinase activity but are also inhibitory to other kinases have also been approved to treat certain cancers. Sunitinib (see above and Table 102e-2) has activity directed against mutant c-Kit receptors (approved for GIST), but also targets VEGFR and PDGFR, and has shown significant antitumor activity against metastatic RCC, presumably on the basis of its antiangiogenic activity. Similarly, sorafenib, originally developed as a Raf kinase inhibitor but with potent activity against VEGFR and PDGFR, has activity against RCC, thyroid cancer, and hepatocellular cancer. Other inhibitors of VEGFR approved for the treatment of RCC include axitinib and pazopanib.

The success in targeting tumor angiogenesis has led to enhanced enthusiasm for the development of drugs that target other aspects of the angiogenic process; some of these therapeutic approaches are outlined in Fig. 102e-12.

EVASION OF THE IMMUNE SYSTEM BY CANCERS

Cancers have a number of mechanisms that allow them to evade detection and elimination by the immune system. These include downregulation of cell surface proteins involved in immune recognition (including MHC proteins and tumor-specific antigens), expression of other cell surface proteins that inhibit immune function (including members of the B7 family of proteins such as PD-L1), secretion of proteins and other molecules that are immunosuppressive, recruitment and expansion of immunosuppressive cells such as regulatory T cells, and induction of T cell tolerance. In addition, the inflammatory effects of some of the immune mediator cells in the tumor microenvironment (especially tissue-associated macrophages and myeloid-derived suppressor cells) can suppress T cell responses to the tumor as well as stimulate inflammation that can enhance tumor growth.

Immunotherapy approaches to treat cancer aimed at activating the immune response against tumors using immunostimulatory molecules such as interferons, IL-2, and monoclonal antibodies have had some successes. Another approach that has shown particular clinical promise is the targeting of proteins or cells (such as regulatory T cells) involved in normal homeostatic control to prevent autoimmune damage to the host but that malignant cells and their stroma can also use to inhibit the immune response directed against them. The approach that is furthest along clinically has involved targeting CTLA-4, PD-1, and PDL-1, co-inhibitory molecules that are expressed on the surface of cancer cells, cells of the immune system, and/or stromal cells and are involved in inhibiting the immune response against cancer (Fig. 102e-13). Monoclonal antibodies directed against CTLA-4 and PD-1 are approved for the treatment of melanoma, and additional antibodies

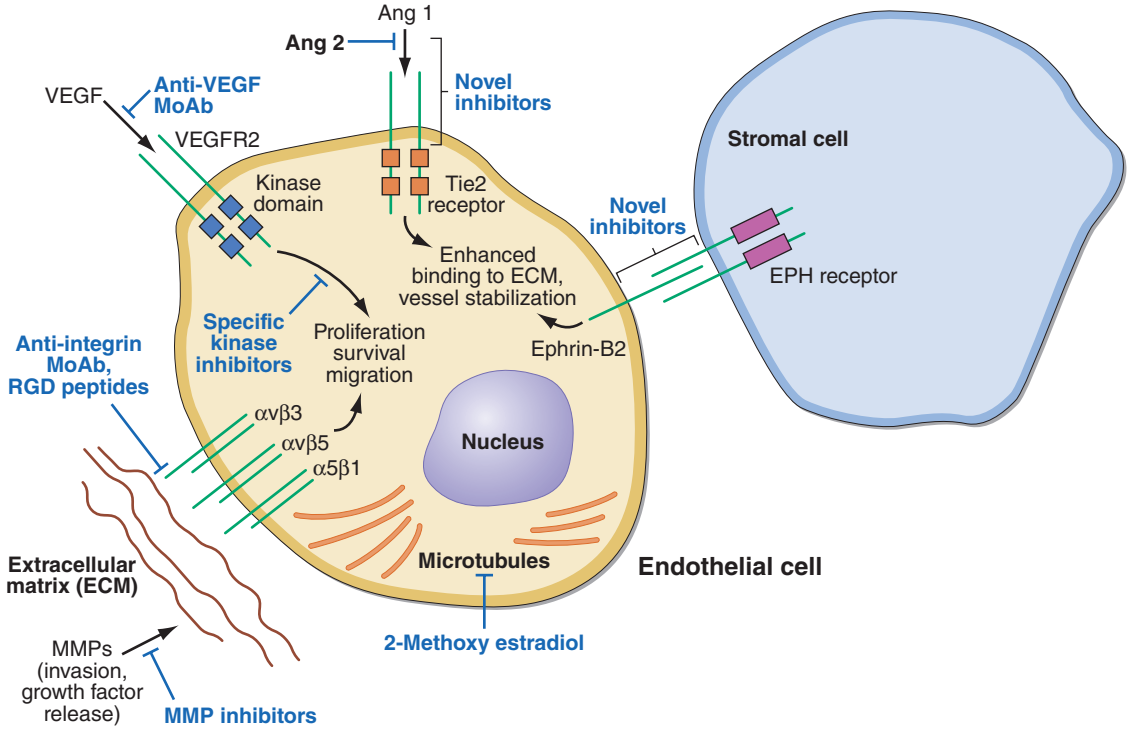

FIGURE 102e-12 Knowledge of the molecular events governing tumor angiogenesis has led to a number of therapeutic strategies to block tumor blood vessel formation. The successful therapeutic targeting of VEGF is described in the text. Other endothelial cell–specific receptor tyrosine kinase pathways (e.g., angiopoietin/Tie2 and ephrin/EPH) are likely targets for the future. Ligation of the $\alpha_v\beta_3$ integrin is required for endothelial cell (EC) survival. Integrins are also required for EC migration and are important regulators of matrix metalloproteinase (MMP) activity, which modulates EC movement through the extracellular matrix (ECM) as well as release of bound growth factors. Targeting of integrins includes development of blocking antibodies, small peptide inhibitors of integrin signaling, and arg-gly-asp–containing peptides that prevent integrin:ECM binding. Peptides derived from normal proteins by proteolytic cleavage, including endostatin and tumstatin, inhibit angiogenesis by mechanisms that include interfering with integrin function. Signal transduction pathways that are dysregulated in tumor cells indirectly regulate EC function. Inhibition of EGF-family receptors, whose signaling activity is upregulated in a number of human cancers (e.g., breast, colon, and lung cancers), results in downregulation of VEGF and IL-8, while increasing expression of the antiangiogenic protein thrombospondin-1. The Ras/MAPK, PI3K/Akt, and Src kinase pathways constitute important antitumor targets that also regulate the proliferation and survival of tumor-derived EC. The discovery that ECs from normal tissues express tissue-specific "vascular addressins" on their cell surface suggests that targeting specific EC subsets may be possible.