Most cancers express tumor antigens that can be recognized by T cells of the host. The fact that cancers that become clinically relevant grow nonetheless implies that immune escape must occur to allow cancer outgrowth. We have observed two major subsets of human melanoma metastases based on gene expression profiling and confirmatory assays. One subgroup of patients has an inflamed phenotype that includes expression of chemokines, T cell markers, and a type I IFN signature. In contrast, the other major subset lacks this phenotype and appears to display immune “exclusion”. Similar subsets have been observed in other cancers, including head and neck cancer. The mechanisms of immune escape are likely distinct in these two phenotypes, and therefore the optimal immunotherapeutic interventions necessary to promote clinical responses may be different. The T cell-inflamed tumor microenvironment subset shows the highest expression of negative regulatory factors, including PD-L1, IDO, and FoxP3+ Tregs, and evidence for T cell-intrinsic anergy has also emerged aided by a recently defined functional role of EGR2. In addition, the mechanism of induction of these inhibitory mechanisms has been elucidated—PD-L1 and IDO are induced by IFN-γ, and Tregs are largely recruited by the chemokine CCL22, both being produced by activated CD8+ effector T cells. Preclinical experiments have confirmed a critical role for each of these mechanisms in limiting anti-tumor T cell efficacy in vivo, giving candidate treatment strategies for translation back into the clinic. These include anti-PD-1/PD-L1 mAbs, IDO inhibitors, and approaches to deplete CD25+ Tregs and/or reverse anergy. The presence of multiple inhibitory mechanisms in the same tumor microenvironment argues that combination therapies may be advantageous. Preclinical data have indicated synergy between anti-CTLA-4 +/- anti-PD-L1 +/- IDO inhibition. The mechanism of synergy is striking, as it correlates with a marked improvement of IL-2 production and proliferation of tumor-infiltrating CD8+ T cells. Clinical translation of multiple combination immunotherapies is promising and ongoing. In contrast to the T cell-inflamed melanomas, a new paradigm may be needed to promote de novo inflammation in cases of the non-T cell-infiltrated tumor microenvironment. Natural innate immune sensing of tumors appears to occur via the host STING pathway, type I IFN production, and cross-priming of T cells via CD8α+ DCs. New strategies are being developed to engage or mimic this pathway as a therapeutic endeavor, including novel STING agonists. The molecular mechanisms that mediate the absence of the T cell-inflamed tumor microenvironment in patients are being elucidated using parallel genomics platforms and should open up additional new treatment approaches to ultimately expand the fraction of patients who respond to immunotherapies. The first oncogene pathway identified that mediates immune exclusion is the Wnt/β-catenin pathway, which argues that new pharmacologic strategies to target this pathway should be developed to restore immune access to the tumor microenvironment.