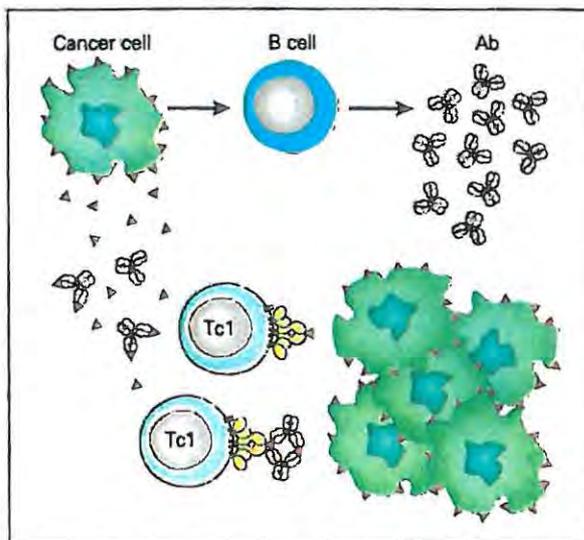**Figure 20-12.** Schematic representation of the killing of a cancer cell, which expresses a TSA by an antibody-complement mediated reaction by antibody directed to a TSA molecule.

cells); and (3) CD4+TGF-β+ T cells that are also induced Treg cells activated in the periphery in the context of oral tolerance and are termed TH3 cells. As will be described in greater detail below, regulatory T cell-mediated immunosuppression is one of the crucial tumor immune-evasion mechanisms and the main obstacle to successful tumor immunotherapy.

Figure 20-13. Schematic representation of the inhibitory effects of antibody or TSA-antibody complexes on the killing of a cancer cell by a CTL killing (blocking antibody).

Role of Antibodies in Tumor Immunity

In addition to their indirect beneficial role in the ADCC mechanism of tumor killing, antibodies can also play a direct role in tumor immunity. Antibody directed to TAA can either facilitate the killing of a tumor cell or paradoxically be responsible for its enhanced growth. Antibody directed to TAA together with activation of the complement system can kill the cancer cell by the cytolytic activation of the membrane-activation complex (MAC) cascade (Figure 20-12 and *Chapter 4*). Alternatively, TAA alone or complexed with antibody as antigen-antibody complexes can interfere with the CTL killing of a cancer cell by blocking its activity (Figure 20-13). As will be described in greater detail below, another mechanism by which CTLs may be blocked is through the excess production of soluble TNF-α receptors (s-TNF-Rs).

Mechanisms of Tumor Cell Evasion of the Immune Response

Possible Survival Mechanisms Used by the Cancer Cell to Evade the Immune System

From what has been presented thus far, it is clear that a number of potential mechanisms may underlie the capacity of a malignant cell to avoid destruction at the hands of the immune system. As described earlier, the immune system is unlikely to be the only defense bulwark against malignancy, so that tumor growth might not be exclusively related to evasion of the tumor by the immune system. The countermeasures that a tumor may employ include downexpression of potential target antigens and inhibition of the T cell response and direct modulation of proinflammatory cytokines, as will described below. These evasion mechanisms may serve as novel targets for cancer therapy.

Tumor Necrosis Factor (TNF)

Tumor necrosis factor-alpha (TNF-α) and lymphotoxin (LT-α or TNF-β) are two interrelated members of the TNF family that, in native form, are homotrimers of 17 and 17.5 kDA peptides, respectively (*Chapter 9* and Figure 20-14). Their genes are located adjacent to one another within the class III major histocompatibility complex (MHC) region in mammals (*Chapter 10*). While LT-α is predominantly produced by lymphocytes, TNF-α is produced by macrophages, lymphocytes, and other cells in selected situations. These cytokines have many in vitro effects that
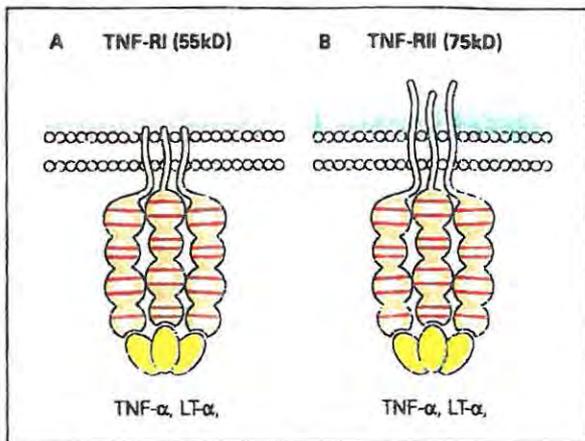
Figure 20-14. Schematic representation of the general structures of the various members of the TNF cytokine family. TNF-α and TNF-β (LT-α) are the best-recognized forms that exist in trimeric form and that attach to their respective trimeric receptors (TNF-R and LTR). There are two receptors that bind TNF-α, called TNF-RI and TNF-RII.

include growth inhibition or lysis of transformed cells, activation of phagocytic cells, upregulation of various cell surface proteins, particularly growth factors, and control of the development and expression of cell-mediated antitumor immune responses. They also display a wide spectrum of reactions in vivo, some of which include necrosis of tumors, leukocytosis and inflammation, cachexia, and shock. Their biologic effects are induced by their engagement with their specific cell surface receptors (*Chapter 9*). The activities attributed to these cytokines have evoked considerable interest for their potential use as anticancer agents. A human recombinant interleukin-2 product, aldesleukin, for example, has been licensed for the treatment of adults with metastatic renal cell carcinoma (RCC) and metastatic melanoma (*Chapter 11*). Although TNF-α would seem to be a potentially optimal antitumor therapy, clinical trials to date indicate that systemically administered TNF-α so as to achieve biologically effective supraphysiologic concentrations in blood has at best limited clinical efficacy and considerable unacceptable toxicity.

TNF Receptors/Inhibitors

Of the more than 20 proteins that comprise the TNF receptor (TNF-R) family, two clinically important TNF receptors are TNF-RI (55 kD), expressed by most cell types, and TNF-RII (75 kD), restricted to lymphoid cells (*Chapter 9* and Appendix 2). These two distinct families of TNF receptors are found either on

cell surfaces or, when released, as extracellular soluble TNF Receptors (sTNF-Rs). The soluble form of the receptor is a truncated version of the membrane TNF-R consisting of its extracellular binding domain and is found in blood and in body fluids. These sTNF-Rs are expressed constitutively and, when released by the malignant cell, are thought to be another form of tumor evasion by their capacity to bind to TNF-α and to inhibit its activity in the surrounding microenvironment of an immune target. Both of these soluble receptors are present in increased levels in the sera of patients with malignancies. There is now evidence that this increase in serum levels above normal constitutive levels is due to their excessive production by cancer cells and/or tumor vasculature and that inhibition of TNF-α/LT by these soluble receptors may be a mechanism by which tumors escape the immunosurveillance system. The removal of soluble cytokine inhibitors present in the plasma of patients with a variety of cancers, might, therefore, be a unique therapeutic intervention leading to tumor regression by increasing local tumor destructive inflammatory responses while sparing systemic effects. The prospective clinical studies by Langkopf and Atzpodien support this putative tumor protective effect and have demonstrated an inverse relationship between patient survival and levels of soluble TNF receptors in blood. More recent clinical studies by Lentz, employing immunoadsorbent methods of TNF-R removal from plasma, have provided further evidence that a variety of tumor types are susceptible to immunologic destruction mediated by TNF-α after the removal of these sTNF-Rs surrounding the tumor (Figure 20-15). The overproduction of TNF-α (originally called "cachexin") and other proinflammatory cytokines may also be the mechanism for the systemic effects of fever, weight loss, malaise, and cachexia seen in cancer patients with extensive disease.

General Concepts of the Role of the Immune System and Inflammation in Tumor Immunity or Progression: Beneficial or Detrimental Outcomes

The immunologic events involved in tumor immunity in many respects are the same as those marshaled in response to infectious agents. Acute activation of innate immunity sets the stage for subsequent activation of the more sophisticated adaptive immune responses. Induction of efficient primary adaptive immune responses requires direct interactions with
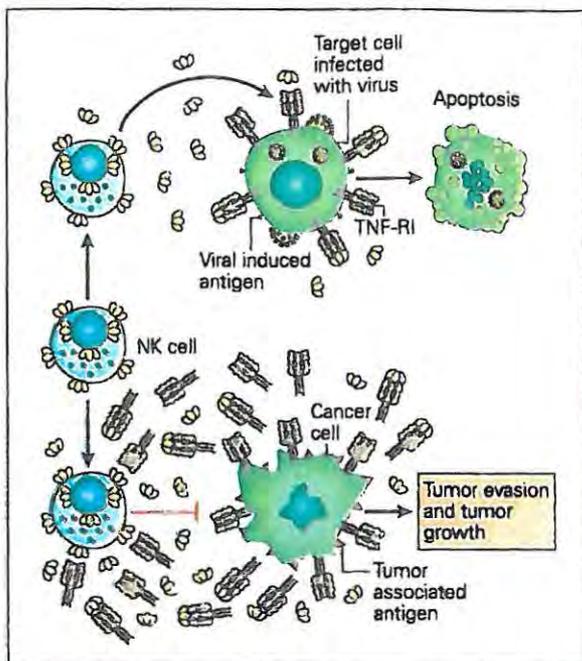
Figure 20-15. Schematic representation of the proposed normal killing mechanisms of a tumor cell by a TNF-producing activated CTL compared to inhibition of TNF killing resulting from its neutralization by excessive production of sTNF-Rs in the surrounding microenvironment of the tumor cell. (Adapted with permission from Dr. M. Rigdon Lentz, MD.)

mature antigen-presenting cells and a proinflammatory milieu. Nonetheless, there is accumulating evidence to suggest that a perturbed innate/adaptive immune balance as seen in chronic inflammation or chronic infection may also enhance conditions for tumorigenesis. The molecular mechanisms that underlie harmful, excessive stimulation of immune cell responses are numerous and complex. Genetic predisposition underlies some disorders, such as pancreatitis, ulcerative colitis, and some rheumatoid diseases. Others are associated with infectious disease pathogens that are able to evade natural tissue immune clearance mechanisms and persist. For example, *Helicobacter pylori*, a Gram-negative bacterium, causes chronic gastritis in infected hosts and in some patients may be associated with gastric cancer, e.g., adenocarcinoma and lymphoma, whereas infection with hepatitis B or hepatitis C virus (HBV and HCV, respectively) is linked to chronic hepatitis, cirrhosis, and in some patients with subsequent development of hepatocellular carcinoma. Similarly, infection with HPV has been associated with vulvar squamous cell carcinomas and adenocarcinomas. Unresolved inflammation resulting from exposure to

toxic factors such as asbestos or smoking, as well as from ongoing chemical or physical irritation, such as acid-reflux disease or exposure to ultraviolet (UV) light, may therefore be related to the development of lung cancer, gastroesophageal junction cancer, and skin cancer, respectively. Mutations and/or genetic polymorphisms in crucial genes that regulate cytokine function, metabolism, and leukocyte survival have also been implicated as etiological factors in chronic inflammation, thus lending further support for the possible relationship of chronic inflammation and cancer.

During acute inflammation, innate immune cells, including phagocytic cells and NK cells, form the first line of immune defense and regulate subsequent activation of adaptive immune responses. By contrast, during chronic inflammation, these roles can be reversed—i.e., adaptive immune responses can cause ongoing and excessive activation of innate immune cells. In arthritis, for example, activation of T and B lymphocytes results in antibody deposition into affected joints, prompting recruitment of innate immune cells into tissue. Once within the tissue, activation and/or degranulation of mast cells, granulocytes, and macrophages, in combination with humoral immune responses, leads to joint destruction. By contrast, whereas acutely activated innate immune cells contribute to efficient T cell activation, chronically activated innate immune cells can cause T cell dysfunction through the production of reactive oxygen radicals.

Regardless of the underlying initiating cause or pathogenetic mechanism, if an infectious or assaulting agent is inadequately cleared and persists in tissue, or a tissue is subjected to ongoing insult and damage that fails to heal in a timely manner, host inflammatory responses can persist and exacerbate chronic tissue damage, which can cause primary organ dysfunction and systemic complications.

Shown in Figure 20-16 is a schematic representation of the hypothetical sequelae of progressive pathogenetic events that occur during the emergence of a cancer. It is the same sequence of events described previously in other chapters for failure of elimination of an infectious agent or foreign substance now applied to a malignancy. In this general synthesizing scheme, failure of elimination of the foreign substance leading to its persistence resulted in inflammation, immunopathology seen in chronic microbial infection (*Chapters 12, 13, 14, and 15*), or autoimmune disease (*Chapter 19*); in the case of cancer, this failure of elimination would lead to further malignant progression and cancer expansion. It may
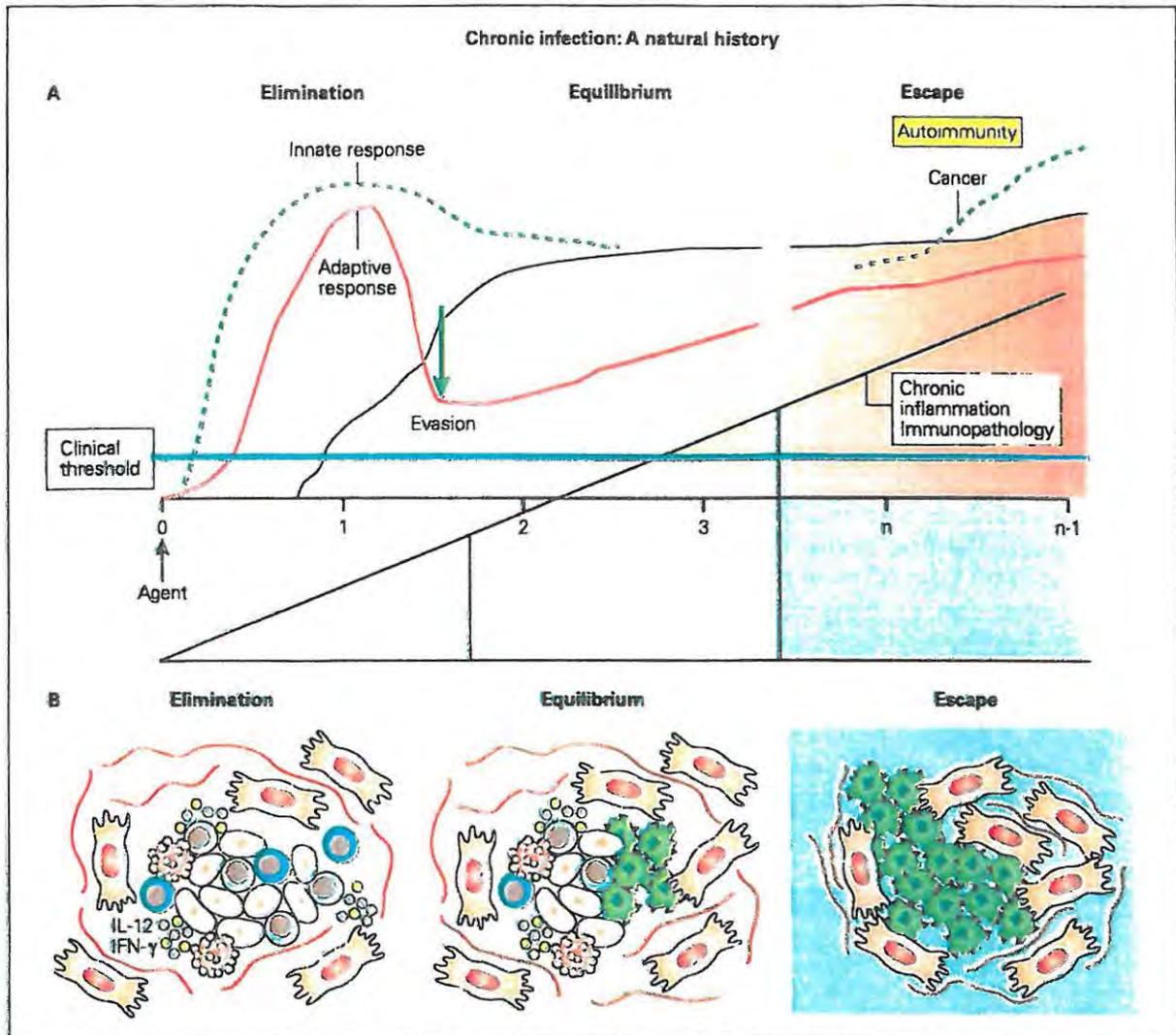
Figure 20-16. Panel A: Schematic representation of the sequelae of pathogenetic events that follow from failure of elimination of an infectious agent or foreign substance, leading to persistence of the foreign configuration with resultant inflammation, immunopathology in the form of autoimmune disease, or malignancy. Panel B: The three phases of cancer immunoediting: elimination, equilibrium, and escape correlated with the morphologic assessment of emerging cancer cells during these various stages. During the first phase of elimination, only normal cells are seen (red); the few malignant cells that emerge are removed by apoptosis; during equilibrium, both normal cells (red) are seen as cancer cells appear (green); during escape, a predominance of cancer cells are seen (green), with no normal cells evident.

now be possible to superimpose the "three Es of cancer immunoediting," i.e., elimination, equilibrium, and escape, upon the three progressive stages of the immune response evolving from innate and adaptive immunity and terminating in the chronic irreversible phase of cancer. During the first phase of immunoediting, i.e., **elimination**, the innate immune response would play the primary role in eliminating the greater part of emergent cancer cells through apoptotic cell death; in the second phase of **equilibrium**, the adaptive immune response would be partially effective in containing

tumor progression and would result in one population of tumor cells capable of being detected by an effective T and B cell response as well as a second emerging population of tumor cells that has learned how to escape immune detection and is being "sculpted" by a futile attempt of an ineffective adaptive immune response; the failure of the immune struggle with the cancer cell would be seen in the third phase of **escape** of immunoediting during which no immune killing would be possible and only further cancer expansion would be seen (Figure 20-16).