SUMMARY

A large body of evidence supports the notion that both the adaptive and nonadaptive immune systems play an important role in the control of tumor progression in patients with malignant disease. These findings have provided the rationale for the development of active specific immunotherapy for the treatment of malignant disease. The enthusiastic application of active specific immunotherapy in a large number of patients has conclusively shown that:

1. Several of the immunization strategies used elicit a tumor antigen (TA)-specific immune response.
2. The results of immunomonitoring assays in patients treated with active specific immunotherapy have poor, if any, predictive value of clinical responses.
3. Irrespective of the TA or immunization strategy used, clinical responses have only occasionally been observed.
4. Disease frequently progresses and recurs in spite of induction and/or persistence of TA-specific immune responses.

These disappointing findings are likely to reflect, at least in part, the ability of tumor cells to manipulate the ongoing TA-specific immune response as well as evade immune recognition and destruction, utilizing multiple mechanisms. The latter include tumor cell-induced qualitative and/or quantitative defects in the generation and maintenance of TA-specific immune responses, tumor cell-induced immune suppression, and/or changes in the antigenic profile of tumor cells because of their genetic instability. These topics are reviewed in this chapter, following a brief description of the essential components of a TA-specific immune response. Lastly, potential strategies to counteract tumor immune suppression and immune escape mechanisms are discussed, because these approaches may improve the outcome of immunotherapy in patients with malignant disease.

**Key Words:** CTL; dendritic cells; HLA class I antigens; immune escape; immune suppression; NK cells; tumor antigens.
1. INTRODUCTION

During the last three decades, a large body of evidence has accumulated to provide support for the concept that the host immune system interacts with developing tumors and, in some cases, may be responsible for the arrest of tumor growth and for tumor regression (1–3). Tumor antigen (TA)-specific T-cells have been shown to play an active role in eliminating tumors and metastases, as well as in inducing TA-specific T-cell memory responses in a wide range of animal tumor models (1). Similarly, in vitro studies employing human peripheral blood lymphocytes isolated from patients with malignant diseases have been reported to contain TA-specific CD8+ and CD4+ T-cell precursors (4–7), as well as natural-killer (NK) cells (8) and macrophages (9) that are capable of killing tumor cell targets after appropriate in vitro activation. These findings, along with (a) the lack of effective treatment for advanced stage malignancies by conventional therapies (10,11); (b) the identification and molecular characterization of TA (12); (c) the development of highly specific probes, i.e., monoclonal antibodies (MAbs) (13) and cytotoxic T-lymphocytes (CTLs) (14); and (d) the development of effective immunization strategies (15,16) have provided the rationale for the development and application of immunotherapy for the treatment of malignant disease.

A large number of active-specific immunotherapy trials have been conducted in patients with malignant disease to date (7,17). It is clear from these studies that vaccines are able to induce and/or augment already established TA-specific immunity, that the immune responses generated against the tumor are far more specific than those elicited by cytokines alone, and that the various types of vaccines have limited or no toxicity. However, clinical responses have been the exception more than the rule. In fact, the general evidence has been that the results of immunomonitoring assays in patients receiving TA-specific vaccines have poor, if any, predictive value, and that lack of clinical response and/or recurrence of disease occurs frequently, in spite of induction and/or persistence of TA-specific immune responses (7). It is worth noting that a majority of the immunomonitoring assays utilized in patients treated with active specific immunotherapy have primarily made use of assays that quantify and characterize the T-cell response to immunizations and have not made any attempt to assess the effect of microenvironment on TA-specific immune responses and to monitor tumor cell susceptibility to TA-specific T-cell immune responses (18). It still remains to be determined when and how patients’ immune response should be assessed and whether ex vivo functional evaluation of peripheral T-cells provides an accurate representation of what is occurring at the tumor site. In retrospect, the lack of correlation between immune response and clinical response observed in patients treated with active specific immunotherapy is not surprising, because the results of these assays do not take into account a patient’s tumor cell susceptibility to recognition by T-cells and to lysis by T-cells. In addition, the in vitro expansion of epitope-specific CD8+ T-cells may not accurately reflect in vivo immune responsiveness, because their in vitro expansion is dependent on their exposure to arbitrarily high concentrations of antigen and exogenous cytokines. The latter may exaggerate the extent of the immune responses ongoing in vivo.

During the past 10 yr, it has become apparent that, in vivo, tumor cells have evolved multiple means to resist and/or hide from immune effector mechanisms (19–23). The latter include tumor cell-induced qualitative and/or quantitative defects in the generation and maintenance of TA-specific immune responses, changes in the antigenic profile of tumor cells because of their genetic instability and/or the potential negative impact of the tumor...