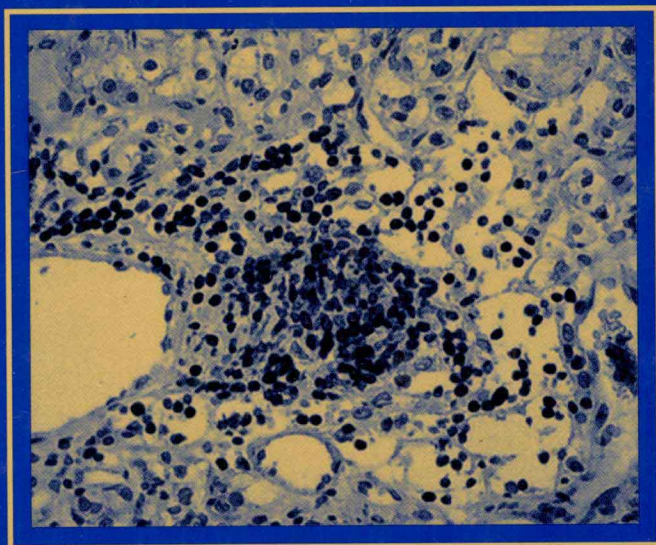

Cancer Immunotherapy at the Crossroads

How Tumors Evade Immunity
and What Can Be Done

Edited by

James H. Finke, PhD

Ronald M. Bukowski, MD



CANCER IMMUNOTHERAPY AT THE CROSSROADS

*HOW TUMORS EVADE IMMUNITY
AND WHAT CAN BE DONE*

Edited by

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and

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Dedication

This book is dedicated to my wife (Jeane) and to my parents (Lillian and Bill Finke) for their never-ending support and encouragement.

Preface

The immune system plays a critical role in controlling and eliminating infectious organisms, including many pathogenic bacteria and viruses. More controversial has been the debate pertaining to whether the immune system can effectively control tumor growth and metastases. However, many studies suggest that appropriate activation of the immune system can lead to tumor regressions in experimental animal models. Thus, there is significant interest in harnessing the immune system for the treatment of tumors. The main focus of immunotherapy has been on T lymphocytes, since they have been shown to be the major effector cells in various animal tumor models. Removal of T cells typically eliminates the antitumor activity of most therapeutic approaches, while conversely, the adoptive transfer of tumor-reactive T cells mediates regression of malignant lesions. Furthermore, in several histologically distinct types of human tumors, the degree of T-cell infiltrate demonstrated a positive correlation with patient survival, suggesting a role for these cells in controlling malignant growth.

Significant progress has been made in the past several decades in our understanding of the host immune response to tumors. This has included: (1) identification of antigens expressed on human tumors as well as epitopes from these proteins that can serve as targets for the CD4⁺ and CD8⁺ T-cell populations; (2) defining and characterizing antigen presenting cells (e.g., dendritic cells), and the co-stimulatory requirements for effective peptide presentation; (3) identifying the role various cytokines play in regulating cellular and humoral immune responses; and (4) understanding the intracellular signaling pathways that control T and APC differentiation, effector function and survival. There have also been important advances in our ability to monitor antitumor immune responses in tumor-bearing hosts. This has included the use of major histocompatibility complex (MHC)-tetramers to detect antigen-specific T cells in the blood and tumor, as well as the development of techniques to measure cytokine expression by subsets of T cells (ELISPOT, flow cytometry-based intracellular staining, and real-time PCR). These insights are leading to new approaches in immunotherapy, and to more precise ways of assessing the impact that such therapy has on antitumor effector T cells.

Prior clinical trials employing cytokines (IL-2 and IL-12) and interferons alone, or in different combinations, have demonstrated antitumor activity in select sets of patients. Overall, the response rate in patients with advanced disease has been in the 10–20% range. More recent clinical studies using various

vaccine strategies (peptides, peptide-pulsed dendritic cells, etc.) have demonstrated an ability to increase the frequency of tumor reactive T cells in the blood and in tumors. However, in the majority of these trials, the modest antitumor activity observed was not commensurate with the augmented number of effector cells. Although these studies suggest that boosting T cell-mediated antitumor immunity has some clinical activity, it currently is beneficial only to a minority of patients. It seems plausible that the effectiveness of immunotherapy will continue to improve as we develop more effective means of enhancing the appropriate effector cells through our better understanding of the tumor immune response at both the cellular and molecular levels. There is growing evidence, however, that tumors can evade the immune system by multiple mechanisms, each potentially representing a significant barrier to immunotherapy. Thus, understanding these processes may be critical to implementing new and more effective forms of immunotherapy.

It has been well documented that the tumor environment can have a negative impact on the development of an effective antitumor immune response. This concept is illustrated by the fact that a significant number of T cells infiltrating human tumors are functionally impaired in their ability to proliferate and mediate important effector functions. Furthermore, impaired immune function, including unresponsiveness to recall antigens, has been noted in peripheral blood T cells, suggesting that systemic effects can occur in cancer patients. There is also evidence to suggest that the antigen-specific T-cell response to some tumor antigens is impaired.

Part I of *Cancer Immunotherapy at the Crossroads: How Tumors Evade Immunity and What Can Be Done* outlines the basic mechanisms that may be operative in cancer patients that contribute to the poor development of antitumor immune responses. Tumors may escape detection by immune cells owing to defective MHC expression and/or antigen processing by the tumor, or because the tumors fail to migrate or interact with T cells at secondary lymphoid organs. Tumors may also evade the immune system by directly or indirectly modulating the normal activation and signaling cascades of immune cells. Indeed, tumors can alter the differentiation and function of dendritic cells, resulting in ineffective antigen presentation, and hence causing T-cell unresponsiveness or anergy. Thus, the tumor environment can impair both CD4+ helper and CD8+ effector T-cell responses. Also discussed within these chapters is the involvement of immunosuppressive products produced either by the tumor or the immune cells themselves, which are likely responsible for some of the immune dysfunction observed in both the antigen-presenting cells and T cells. It is also becoming clear that the tumor environment may alter the sensitivity of T cells and dendritic cells to programmed cell death, or apoptosis. This may occur as a natural response to antigen, leading to activation-induced cell death, or by the elaboration of tumor products that directly sensitize or induce apoptosis in immune cells.

Several chapters address mechanisms of optimizing antigen presentation and the delivery of T cells to tumor sites as well as ways to promote their survival. These modifications appear to enhance T-cell effector function and may render tumors less capable of immune evasion. Also discussed is the notion that malignant cells utilize some of the same immune escape mechanisms employed by various pathogens, suggesting that lessons learned from the study of infectious diseases may benefit the understanding of immune dysfunction in cancer. Although the majority of mechanisms examined in these pages focus on the tumor-induced dysfunction of immune cells, also included is a chapter appraising molecular alterations within the tumor cells themselves that afford resistance to apoptosis. These modifications enhance not only the resistance of tumors to immune-mediated attack, but also may significantly reduce their susceptibility to radiation and chemotherapy.

Additional chapters address immune dysfunction and evasion mechanisms in histologically diverse human tumors. These chapters highlight both the immunosuppressive tactics common to multiple tumor types, and the unique evasive mechanisms employed by biologically and histologically distinct tumors.

In Part II, the clinical relevance of immune evasion is reviewed. The functional and signaling defects in T cells and antigen-presenting cells and their relation to impaired antitumor immune responses and to poor clinical outcome are discussed. These investigations also ask whether measurably impaired signaling and effector function in T cells may one day serve as biomarkers for patient prognosis. These types of analysis are clearly important and suggest that defects in T cell signaling and immune function impact on clinical outcome, however, more studies are needed to address this issue.

The future development of effective immunotherapeutic protocols for treating cancer will incorporate strategies that can abrogate the mechanisms by which tumors evade the immune system in different histologic types of tumors. It is thus relevant to study and understand these evasion mechanisms in order to devise ways to prevent and/or circumvent their capacity to enhance progressive tumor growth.

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CANCER IMMUNOTHERAPY AT THE CROSSROADS

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I

BASIC MECHANISMS OF IMMUNE EVASION
