

# Preface

Since publication of the first edition of this monograph the field of tumor immunology and immunotherapy made tremendous progress. The second edition reflects those changes. The chapters were revised to reflect new information and several new chapters were added. The development of any field of science follows spiral motion from basic observations to greater understanding of more and more complex mechanisms. Along this road, many basic facts are being rediscovered over time, at new, more sophisticated levels. However, for people outside the field, this spiral motion is usually lost and the movement is often reminiscent of a pendulum. The period of enthusiasm is followed by widespread disappointment to be replaced by the renewed enthusiasm.

Tumor immunology and cancer immune therapy are classic examples of this paradigm. Initial realization that some immune mechanisms could be involved in control of tumor growth and hopes that the treatment of cancer with bacterial pathogens or simple vaccines could cure cancer made tumor immunology an exciting area of research in the first 30 years of last century. However, the period of high expectations was followed by long hiatus of skepticism or even oblivion when clinical results did not meet expectation. Moreover, some experimental results suggested that the immune system was not involved in regulation of tumor progression.

In late 1980s, when the nature of some tumor-associated antigens was identified and researchers discovered limitations of original experimental systems used to determine the role of the immune system in cancer, interest in the field returned. With the identification of many regulatory activities in T cell activation, more molecularly-targeted approaches were described. Many clinical trials were initiated and hopes for quick progress were again high. However, at the beginning of this century, lack of sufficient success in clinical trials turned the pendulum back to skepticism.

Fortunately, this skepticism was placed in very a different environment than in previous years. Much more was learned about the mechanisms by which the immune system responds to tumors and how it is regulated. One of the areas that developed fast during the last 20 years was immune suppression in cancer. Research in this field did not slow down and in recent years, has produced real pre-clinical successes. Now, the field is gaining momentum again. Interest in tumor immunology and immunotherapy is high, and numerous clinical trials are being conducted, with

encouraging results. This includes FDA approval of both a prostate cancer vaccine and a monoclonal antibody which blocks CTLA-4-dependent inhibition. However, despite many positive signs, it is clear that the level of responses is still rather limited and only a fraction of the patients truly benefit from these therapies. One of the major factors that limits the effect of cancer immune therapy is the persistence of suppressive mechanisms that arise in the tumor microenvironment, which limit the durability of anti-tumor immune responses.

This monograph will present readers with a broad and comprehensive overview of these mechanisms. They range from immune suppressive cytokines and molecules expressed by tumor cells to immune suppressive T cells and myeloid cells. Each factor has its own history, elaborate pathway and functional consequences. The litany of mechanisms present in tumor-bearing hosts is so powerful and redundant, that it raises a question how a host can actually survive such an onslaught, given the need for maintaining immunity to pathogens. Importantly, it is well known that neither tumor-bearing mice nor cancer patients are profoundly immune suppressed until very late in tumor progression. Even in that situation, it is not clear whether these consequences are due to specific immune suppressive mechanisms or metabolic changes associated with tumor-induced cachexia. Patients don't suffer from opportunistic infections and could be immunized, albeit with some difficulties, against viral pathogens.

It seems that there are two possible explanation for this paradox. One is that there is a strong compartmentalization of immune suppression associated with cancer. The tumor site provides a profound immune suppressive microenvironment, whereas in peripheral lymphoid organs, non-specific suppression is rather limited and the main operational mechanism is tumor-specific immune tolerance. Several chapters in this book will discuss these issues.

However, there could be another explanation. It is possible that various immune suppressive factors are not that redundant after all and instead, are essentially tumor-specific. In this scenario, a tumor has a "driver" immune suppressive mechanism that determines the outcome of the response and "passenger" mechanisms, which may be present present but not critical. One example is the role of myeloid-derived suppressor cells (MDSC) and regulatory T (Treg) cells in melanoma. In the B16F10 melanoma model, Treg cells play a prominent role whereas MDSCs appear to be a "passenger" factor. The situation is reversed in the Ret transgene-induced melanoma model, where MDSC are the critical "driver" factor determining the suppressive mechanism. This paradigm can be observed in other tumor models where different immune suppressive factors may exert different roles.

Immune suppressive factors are attractive therapeutic targets with a goal of boosting immune responses and enhancing antitumor activity. However, universal approaches to therapeutic correction of the situation may be prone to failure. There is also a risk of targeting redundant or inconsequential suppressive mechanisms which might also have adverse effects to immunotherapy. We need to approach this therapeutic intervention with open eyes to avoid mistakes made in previous years. Therefore future studies should address several major questions.

- There is a need to determine “driver” immune suppression factors for each type of tumor and specific factors that could cause this. This may be used for more precise targeting;
- It may worth considering the creation of a standard diagnostic panel, where major factors of immune suppression are tested in each particular tumor;
- Compensatory changes need to be monitored, with consideration of targeting multiple mechanisms as necessary;
- Monitoring different suppressive mechanisms during relapse.

In recent years, a new paradigm of cancer treatment was developed. It suggests that conventional cancer therapy (radiation, chemotherapy) can synergize with immune-based therapy of cancer. The role of immune suppressive networks in this combinatorial therapy is only beginning to emerge. It is tempting to speculate that elimination of immune suppression could play an important role in this process. However, the results are mainly obtained in tumor-bearing mice and more work needs to be done in the clinical setting, which will give a more realistic validation to the hypothesis. The field of tumor immunology is now engaged in a renaissance, with very high hopes for successful immune therapeutics. However, in order to be successful, we need to revisit our understanding of the regulation of the tumor microenvironment. We believe that this monograph will help readers to do this.

**Tumor-Induced Immune Suppression  
Mechanisms and Therapeutic Reversal**

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