The Immunology of Melanoma

Jennifer S. Ko, MD, PhD

KEYWORDS

• Tumor • Melanoma • Immunology • T cell • Type 1 • Checkpoint • Prognosis • Immunotherapy

KEY POINTS

- Melanoma is thought to be the most immunogenic tumor due to its exceptionally high (UV-driven) mutational burden, which allows for the creation of neoantigens recognizable as "non-self" by host immunity.
- Immune editing refers to the process by which the host immune system modifies the quantity and quality of tumor growth, and by which the tumor adapts to grow under the selective pressure of the immune system. It occurs through 3 phases: immune surveillance/elimination, equilibrium, and escape.
- Brisk tumor-infiltrating lymphocytes are associated with improved survival in melanoma and imperfectly overlap with markers currently under investigation to predict responsiveness to immunotherapy.
- T-cell checkpoint inhibitor drugs break tumor-exploited mechanisms of peripheral tolerance at the T-cell priming phase (CTLA-4, ipilimumab) and the T-cell effector phase (PD-1, nivolumab, pembrolizumab) to produce unparalleled clinical responses in melanoma.
- Current research in melanoma is aimed at identifying (better) markers to predict response to immunotherapy, and at discovery of interventions to render immune-excluded tumors immunogenic and responsive to immunotherapy.

INTRODUCTION

Cutaneous melanoma is a relatively common, potentially lethal skin tumor of increasing incidence, with a propensity to affect relatively young patients, and a highly variable survival among patients with localized disease. It has a propensity for metastasis, with potential for visceral organ spread occurring remarkably early in its growth phase. Hence, melanoma has been the subject of intense research over the past several decades. Immunology is woven throughout the history of cancer, and the story of melanoma, in particular, with powerful prognostic and therapeutic influences.

Department of Anatomic Pathology, Cleveland Clinic, 9500 Euclid Avenue, L2-150, Cleveland, OH 44195, USA
E-mail address: koj2@ccf.org

Clin Lab Med 37 (2017) 449–471
http://dx.doi.org/10.1016/j.cll.2017.06.001 **labmed.theclinics.com**

Indeed, melanoma has paved the way for our understanding of immunotherapy, which now influences many other tumor types, including Merkel cell carcinoma, lung carcinoma, renal cell carcinoma, and many more. The interrelationship between the immune system and malignancy is best understood through the concept of cancer immunoediting, which exists in continuum from immunosurveillance to immune equilibrium to tumor escape. This review discusses the historical background, scientific basis, and clinical implications of melanoma's intricate relationship with host immunity, using the framework of immunoediting.

TUMOR IMMUNOLOGY: HISTORICAL PERSPECTIVE

The history of tumor immunology has been wrought with controversy. More than 100 years ago, Paul Ehrlich[1] initiated a century of contentious debate over immunologic control of neoplasia. He was a pathologist and chemist who won the Nobel Prize in 1908 mostly for his work with antibodies, antisera, and antitoxins. He observed that when tumors in mice were cultivated by sequential transplantation to other mice, their malignancy increased from generation to generation. He also noted that when a primary tumor was removed, the metastasis would precipitously increase. In an analogy to vaccination, he attempted to generate immunity to cancer by injecting weakened cancer cells. Based on his research, Ehrlich proposed in 1909 that tumor cells, due to altered patterns of protein expression, differ from their normal cellular counterparts, and that these differences allow them to be recognized and destroyed by immune cells via a process called immunosurveillance.[1] In 1957, Burnet and Thomas[2,3] formalized this proposal in their cancer immunosurveillance hypothesis, which predicted that the immune system recognizes and eliminates nascent transformed cells, based on "the emergence of a new and therefore foreign antigenic pattern" in cancer. In the same publication, they cited work by Black and colleagues,[4] which found a sharp correlation between the degree of lymphocytic inflammation in surgically removed tumors, and the likelihood of "cure" following surgery. The cancer immunosurveillance hypothesis also postulated that most tumors are eliminated before becoming clinically apparent, and that tumor development is usually suppressed. At the same time, landmark experiments by Old and colleagues[5] showed that inoculation with Bacillus Calmette-Guerin (BCG) was curative of bladder cancer in mice; and this observation has since led to the widespread clinical use of BCG as intravesicular immunotherapy for treating early-stage bladder cancer.[6]

In the following 2 decades, researchers sought to validate the immunosurveillance hypothesis by testing the incidence of spontaneous, chemically induced, or virally induced tumors in various populations of mice. Initial studies, done by Stutman and Rygaard and Povlsen,[7–9] showed that athymic nude mice failed to form more chemically induced or spontaneous tumors than their wild-type (WT) counterparts. Virally induced tumors occurred much more frequently in athymic nude mice, but this was thought to relate to increased viral replication.[10] Although it is now known that the negative results obtained by Stutman and Rygaard and Povlsen[7–9] were likely reflective of several important experimental caveats to their study design, including and not limited to the intact lymphocytes that still circulate in nude athymic mice, enthusiasm vanished for immunosurveillance by 1978, and researchers concluded that the cancer immunosurveillance hypothesis was dead.[11] Instead, the field of tumor immunology began to work on other areas, including defining the molecular nature of tumor antigens and the development of immunotherapeutic strategies for cancer. This abandonment is reflected in the *Cell* publication in 2000 by Hanahan and Weinberg,[12] in which