Progress in Retinal and Eye Research 28 (2009) 329–347

Contents lists available at ScienceDirect

Progress in Retinal and Eye Research

journal homepage: www.elsevier.com/locate/prer

Immune escape mechanisms of intraocular tumors

Jerry Y. Niederkorn

Department of Ophthalmology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9057, USA

Keywords:
Anterior chamber
Immune escape
Immune privilege
Immune surveillance
Metastasis
Natural killer cells
Uveal melanoma

A B S T R A C T

The notion that the immune system might control the growth of tumors was suggested over 100 years ago by the eminent microbiologist Paul Ehrlich. This concept was refined and expanded by Burnet and Thomas 50 years later with their articulation of the "immune surveillance" hypothesis. In its simplest form, the immune surveillance hypothesis suggests that neoplasms arise spontaneously and express novel antigens that are recognized by the immune system, which either eliminates the tumors or restrains their growth. Within the eye, immune responses are controlled and sometimes profoundly inhibited – a condition known as immune privilege. Immune privilege in the eye is the result of a complex array of anatomical, physiological, and immunoregulatory mechanisms that prevent the induction and expression of many immune responses. Tumors arising in the eye would seem to have an advantage in evading immune surveillance due to ocular immune privilege. Uveal melanoma, the most common and malignant intraocular tumor in adults, not only benefits from the immune privilege of the eye but also has adopted many of the mechanisms that contribute to ocular immune privilege as a strategy for protecting uveal melanoma cells once they leave the sanctuary of the eye and are disseminated systemically in the form of metastases. Although the immune system possesses a battery of effector mechanisms designed to rid the body of neoplasms, tumors are capable of rapidly evolving and countering even the most sophisticated immunological effector mechanisms. To date, tumors seem to be winning this arms race, but an increased understanding of these mechanisms should provide insights for designing immunotherapy that was envisioned over half a century ago, but has failed to materialize to date.

Contents

1. Introduction 330
2. Immunoediting: cancer's answer to immune surveillance 330
3. Immune privilege in the eye: fertile ground for tumor growth? 331
   3.1. Anatomical and structural features that contribute to ocular immune privilege 331
   3.2. Cell membrane molecules affecting ocular immune privilege 332
   3.3. Soluble factors that contribute to ocular immune privilege: "There's something funny about aqueous humor" 333
   3.4. Anterior chamber-associated immune deviation: evidence that ocular immune privilege reaches beyond the eye 333
   3.5. In situ induction of ocular regulatory cells 334
   3.6. Relevance of ACAID: why does the eye tolerate an "immunological blind spot"? 334
4. Circumvention of immune privilege and intraocular tumor rejection 335
   4.1. Allogeneic, xenogeneic, and syngeneic intraocular tumor rejection: lessons from three blind mice 335
   4.2. Immune surveillance of uveal melanomas 337
5. Liver metastasis of uveal melanoma: immunoediting of NK cell-mediated immune responses 338
6. Immune escape mechanisms of uveal melanomas: creating ad hoc immune privilege 339
   6.1. Indoleamine 2,3 dioxygenase 339
   6.2. Programmed death ligand-1 339

Abbreviations: AC, anterior chamber; ACAID, anterior chamber-associated immune deviation; CGRP, calcitonin gene-related peptide; CRP's, complement regulatory proteins; MHC, major histocompatibility complex; MIF, macrophage migration inhibitory factor; SOM, somatostatin; TGF-β, transforming growth factor beta; TILs, tumor-infiltrating lymphocytes.

E-mail address: jerry.niederkorn@utsouthwestern.edu

1350-9462/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.preteyeres.2009.06.002

6.3. Complement regulatory proteins 339
6.4. Resistance to perforin-mediated cytolysis 340
6.5. Blockade of FasL-induced apoptosis 340
6.6. Disabling NK cell-mediated immune surveillance 341
7. Does the immune system promote tumorigenesis? 341
7.1. The riddle of tumor-infiltrating lymphocytes and poor prognosis 341
7.2. Myeloid-derived suppressor cells: "Immunological betrayal of the worst kind" 342
8. Future directions 343
Acknowledgments 343
References 343

1. Introduction

The notion that the body might be able to defend itself against neoplasms was demonstrated in the century before last by Coley who noted the beneficial effects of bacterial toxins in the treatment of sarcomas (Coley, 1891, 1893). The responses were probably due to the action of tumor necrosis factor-α (TNF-α), which was undoubtedly present in the bacterial extracts that were used to treat sarcoma patients. In 1909, Paul Ehrlich predicted that the immune system might protect the host from carcinomas (Ehrlich, 1909). However, the absence of intimate knowledge about the immune system and the limited tools for experimental studies prevented Ehrlich from testing this hypothesis. Almost 50 years would pass before Burnet and Thomas would revisit Ehrlich's prediction and articulate their "immune surveillance" hypothesis (Burnet, 1957; Thomas, 1959). Subsequent studies confirmed the presence of tumor antigens on chemically and virally induced neoplasms in rodents and lent credence to the immune surveillance concept (Klein, 1966; Old and Boyse, 1966). Implicit in the immune surveillance hypothesis is the prediction that neoplasms arise spontaneously and are eliminated by the immune system before they reach clinically detectable sizes. Accordingly, one would expect that mice with defective immune systems should experience a significantly elevated incidence of spontaneous tumors or an accelerated appearance of chemically induced neoplasms. However, when this hypothesis was tested in athymic nude mice, which lack fully developed T and B cell repertoires, the mice did not differ from immune competent mice in either the incidence of spontaneous tumors or the development of chemically induced tumors (Stutman, 1974, 1975). As a result, the immune surveillance hypothesis fell into disrepute and languished in the margins of tumor biology for almost two decades. In retrospect we know that although nude mice have defective adaptive immunity, their innate immune responses, especially natural killer (NK) cells, are exceptionally well developed and can contribute to the immune surveillance of tumors. A number of experimental results led to the re-emergence of the immune surveillance hypothesis in the 1990s. The finding that administration of neutralizing antibodies to interferon-γ (IFN-γ) resulted in accelerated tumor growth in rodents and the observation that mice deficient in the IFN-γ receptor displayed an increased frequency of chemically induced cancers resurrected interest in the concept of immune surveillance (Kaplan et al., 1998; Shankaran et al., 2001). Other studies showed that the absence of the gene encoding perforin, a key enzymatic protein involved in cytolysis by cytotoxic T lymphocytes (CTLs) and NK cells, resulted in an increased incidence of spontaneous B cell lymphomas in mice (Smyth et al., 2000). Moreover, mice deficient in NK cells and NKT cells were also found to be more susceptible to spontaneous tumors and the accelerated growth of transplanted tumors (Dunn et al., 2006; Smyth et al., 2006). One of the nagging arguments against the immune surveillance hypothesis stems from the observation that animal studies have largely relied on either chemically induced tumors or transplanted tumors. A convincing rebuttal to this criticism arose from studies in mice lacking the recombination-activating gene-2 (RAG2), which is necessary for the generation of immunoglobulin and T cell receptor rearrangements. These mice lack T cells, B cells, and NKT cells. RAG knockout (KO) mice crossed with mice bearing a mutant form of the p53 tumor suppressor gene have a significantly increased incidence of spontaneous tumors, which provides compelling evidence that elements of the adaptive immune system monitor and restrict the development of spontaneous tumors, a condition that mimics what Burnet and Thomas envisioned over 50 years ago (Liao et al., 1998; Nacht and Jacks, 1998).

A crucial tenet of the immune surveillance concept is that patients with underlying immune deficiencies should experience an elevated incidence or an accelerated progression of tumors. Circumstantial evidence suggests that this is the case. Individuals with acquired or hereditary immune deficiencies experience a higher than normal incidence of virally associated and carcinogen-associated cancers, and organ transplant recipients who are subjected to long-term immunosuppressive drugs have a 3–8-fold increase in the incidence of neoplasms (Reiman et al., 2007; Swann and Smyth, 2007). In the case of kidney transplant patients, there are reports of 2–5-fold increases in cancers of the colon, lung, bladder, prostate, and a 30-fold increase in skin cancers and kidney cancers (Birkeland et al., 1995). Likewise, the risk of melanoma doubles in organ transplant patients (Penn, 1996). The innate immune system also appears to play a role in immune surveillance, as patients with Chediak Higashi syndrome, a condition that results in severe impairment of NK cell-mediated cytotoxicity, have a 200-fold increase in their risk for developing cancer (Kobayashi, 1985). Thus, both experimental and clinical data support the notion that the immune system can monitor the development and control the outgrowth of cancers in both humans and animals.

2. Immunoediting: cancer's answer to immune surveillance

Although the evidence supporting immune surveillance of cancer is compelling, the battle between the immune system and cancer is not one-sided. The mere fact that cancer remains a major cause of morbidity and mortality is a testament to the imperfections of immune surveillance. In fact, there are some who suggest that under some conditions, the immune system might unwittingly contribute to tumor development. This concept was raised almost 40 years ago by Prehn who proposed that the immune system might stimulate, rather than inhibit, tumor growth (Prehn, 1972). Prehn suggested that a "weak" immune response stimulated tumor growth, while more intense immune responses controlled tumors. Consistent with this is the time-honored observation that chronic inflammation is associated with an increased risk of cancer (Balkwill et al., 2005). Moreover, the use of anti-inflammatory drugs to treat chronic inflammatory diseases is associated with a reduced risk for cancer (Dannenberg and Subbaramaiah, 2003). It is clear