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Review

Tumor immunoediting and immunosculpting pathways to cancer progression

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Abstract

Recent studies have suggested that a natural function of the immune system is to respond and destroy aberrant, dysfunctional cells by a process called immunosurveillance. These studies also suggest that the tumors that arise despite immunosurveillance have been immunosculpted by the immune system. The purported abilities of tumors to induce immune tolerance and suppression, the increased pathogenic behavior of the tumor cells following exposure to immune effectors and the loss of immunogenicity (i.e. immunoediting) often observed in advanced stage tumors could be the result of immunosculpting. In some cases, these immunosculpting features may be permanent and irreversible. However, in other cases, reversible epigenetic mechanisms may underlie the immune resistant tumor phenotype. Regardless, these immune-induced alterations could contribute to cancer pathogenesis. Understanding the mechanisms by which tumors evade immunity will be important for disease prevention and therapeutics.

Keywords: Immunosurveillance; Tumor immunity; Vaccines; Adoptive T cell therapy

Contents

1. Introduction 275
2. The immune system and immunosurveillance 276
   2.1. Immunosurveillance in mouse models 276
   2.2. Circumstantial evidence in humans supports immunosurveillance 276
      2.2.1. Tumors attract in immune cells very early in the course of disease 276
      2.2.2. Patients generate immune responses to tumor antigens, which correlate with disease outcome 277
      2.2.3. The immunosuppressed have an elevated cancer risk 277
3. The paradoxical roles of the immune system in malignancy 277
   3.1. The immune system is linked to tumor development and progression 277
      3.1.1. Immunosculpting and immunoediting 278
   3.2. Immunoediting in immune-based therapeutics 282
   3.3. Preventing and overcoming immunosculpting and immunoediting during immunotherapy 283
      3.3.1. Targeting multiple antigens 283
      3.3.2. Targeting MHC-defective tumors 283
      3.3.3. Blocking epigenetic mechanisms 283
4. Conclusions 284
   Acknowledgements 284
   References 284

1. Introduction

It has been proposed by several investigators that a natural function of the immune system is to seek out and eradicate aberrant (dysplastic and neoplastic) cells and tissues so that tumors

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will not form. If true, then in cases where tumors have emerged, the immune system has apparently failed due to immune tolerance or escape. As some studies suggest, interactions between the tumor and the immune system following immunosurveillance may result in sculpting of the tumor for increasingly aggressive growth and further resistance to immune destruction. The heterogeneous immune escape strategies and immune effector content of human tumors, as well as the unpredictable responses of tumors to immunotherapies, suggests that there may be considerable diversity in tumor:immune interactions. Understanding these interactions could lead to improved design of immunotherapies and more appropriate clinical testing. In this review, the focus is on the idea that tumor development and phenotype are a reflection of past interactions of the tumor and the immune system.

2. The immune system and immunosurveillance

The concept of immunosurveillance was proposed several decades ago, but it is only recently that the theory has been rigorously examined. With the advent of knockout technologies, immunosurveillance has been directly demonstrated in mice. In humans, sophisticated assays and improved population sciences have provided compelling indirect evidence.

2.1. Immunosurveillance in mouse models

Murine models of spontaneously arising or chemically induced tumors have been useful in demonstrating that the immune system naturally surveys for aberrant cells and has an important role in preventing tumor formation. The landmark study that invigorated interest in immunosurveillance by demonstrating important anti-tumor roles of IFN-γ and lymphocytes was reported by Shankaran et al. [1]. In that study, mice were used that were insensitive to IFN-γ either by knocking out the IFN-γ receptor α chain, or the IFN-γ-inducible downstream transcription factor, STAT1. The key observation was an increase in 3-methylcholanthrene (MCA)-induced sarcoma development in the IFN-γ insensitive mice relative to wild-type mice. Mice that lack both B and T lymphocytes (i.e. RAG2$^{-/-}$), were also highly susceptible to chemically induced tumor development, at similar rates compared to that of IFNγR$^{-/-}$ and STAT1$^{-/-}$ mice. Crossing the RAG2$^{-/-}$ and the STAT1$^{-/-}$ mice (RkSk mice) further enhanced tumor incidence, suggesting that multiple, yet non-overlapping, mechanisms contribute to immunosurveillance. Aged RkSk mice also demonstrated a high incidence of spontaneous tumor development compared to age-matched control. Studies from other groups using perforin knockout mice suggest, as expected, that cytotoxic cells (NK, NKT and cytotoxic CD8 T lymphocytes, CTL) are among the major lymphocyte contributors to immunosurveillance. Perforin deficient mice have reduced ability to control development of transplanted tumor; increased susceptibility to sarcoma development following chemical exposure [2], and increased spontaneous lymphoma development [3]. Another molecule expressed by cytotoxic T cells that has recently shown to be involved in immunosurveillance is TRAIL, a transmembrane protein of the TNF family [4–10]. TRAIL preferentially induces apoptotic cell death in transformed cells but not in normal cells *in vitro*, a finding that further supports the notion that the immune system has evolved mechanisms to specifically deal with neoplastic cells [11]. Several other immune effector cells and molecules have been directly knocked out to demonstrate their respective roles immunosurveillance in mice, including natural killer (NK) cells, NK-T cells [12,13], γδ T cells [14,15], IL-12 [16], granulocyte-macrophage colony-stimulating factor (GM-CSF) [17], and α-galactosylceramide (α-GalCer) [18].

2.2. Circumstantial evidence in humans supports immunosurveillance

Natural immunosurveillance is difficult to examine in human cancers. Despite this, there have been studies over the past decade that provide compelling, albeit indirect, evidence. These studies can be roughly classified into three major areas of study; infiltration of tumors with immune effectors, the generation of endogenous immunity to tumor antigens, and the observations that patients with immune deficiencies demonstrate abnormal risks for cancer development.

2.2.1. Tumors attract in immune cells very early in the course of disease

Infiltration of immune effectors is a well-documented observation in most if not all cancers. Emerging studies now reveal that infiltration occurs very early in the course of disease. In benign proliferative disease of the breast, a pre-breast cancer lesion, 30-fold increases in T cell infiltration have been observed and this level remains fairly constant throughout the course of progression into invasive breast cancer [19]. In many cases, T cell infiltration correlates with disease outcomes. One of the cornerstone studies demonstrating a biologic role for tumor-infiltrating T cells came from Zhang et al. with their analysis of infiltrating T cells in 186 frozen ovarian cancer specimens [20]. Of the 186 patient samples, 102 (54.8%) lesions had CD3 T cells infiltrating the tumor parenchyma, and there were significant differences in the distributions of progression free and overall survivals according to the presence or absence of infiltrating T cells. The median overall survival rate for patients with intratumoral T cells was 38% compared while only 4.5% for patients without detectable infiltrating T cells. In those patients who had a complete clinical response to surgery and chemotherapy the differences in median survival was more pronounced, with a median survival of 74% in patients with intratumoral T cells and 11.9% in those without intratumoral T cells. In a follow-up study by Sato et al., it was found that those ovarian cancer patients that had high levels of CD8 T cells infiltrating into the tumors had an improved outcome relative to those with lower levels [21]. Similarly, infiltrating T cells were associated with improved survival in colorectal cancer patients [22,23]. In colorectal cancer, immune effectors may protect against disease progression, since the lack of immune infiltration is associated with the development of metastases [22].