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Mechanisms of the self/non-self-survey in the defense against cancer: Potential for chemoprevention?☆

Ricky A. Sharma[a,b,*], Michael J. Browning[c]

[a] *Radiotherapy Department, Royal Marsden Hospital NHS Trust, Downs Road, Sutton SM2 5PT, UK*
[b] *Oncology Department, Leicester Royal Infirmary, University of Leicester, Leicester LE2 7LX, UK*
[c] *Department of Infection, Immunity and Inflammation, University of Leicester, Maurice Shock Building, University Road, Leicester LE1 9HN, UK*

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☆ In a review of this breadth, it has been impossible to refer to all the relevant publications. We apologise to those colleagues whose papers we have been unable to cite because of limitations on space.

* Corresponding author. Tel.: +44 208 642 6011; fax: +44 208 661 3127.
E-mail address: ras20@le.ac.uk (R.A. Sharma).

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Abstract

When compared to a reference population, several large epidemiological studies with long-term follow-up have reported a three- to five-fold increased risk of neoplasia amongst patients who have received organ transplants, with an incidence curve that rises in a linear fashion with time. The relationship between the immune system and cancer is complex. The ability to discriminate "self" from "non-self" is one of the central roles of the immune system. Since tumors arise from transformation of host cells, it is not surprising that some aspects of tumor immunity resemble autoimmunity. The immune response to tumors shares aspects of both self- and non-self-immune recognition. What accounts for the apparent failure of immunity? In this review article, we address the role of the self/non-self-survey in the immune response to tumors, we describe mechanisms of immune surveillance against tumor cells, and we discuss models of ignorance, tolerance and tumor evasion of the immune response. The overall aim of the article is to demonstrate the scope for prevention of cancer in individuals at increased risk of developing malignancy due to immune compromise. Interventional strategies may involve the use of pro-differentiation agents such as retinoids, modifiers of polyamine biosynthesis or inhibitors of cyclooxygenase isozymes.

Keywords: Immune surveillance; Immunotherapy; Prevention

1. Introduction

The relationship between the immune system and cancer is complex, and has been the subject of much controversy. Central to this has been the validity of the "immune surveillance theory," by which the immune system recognizes and eliminates cells undergoing oncogenic transformation, and the extent to which self/non-self-discrimination limits immune responsiveness to emerging tumors. The ability to discriminate "self" from "non-self" is one of the central roles of the immune system. Indeed, the repertoire of antigens to which the adaptive immune system can respond is shaped within the individual by clonal deletion of T and B cells with high affinity antigen receptors for self-antigens in primary lymphoid tissues, whilst those with relatively low affinity to self, but the potential to respond to non-self, are positively selected and released into the periphery. The process is clearly imperfect, as the relatively high incidence of autoimmune diseases attests. However, the basis of self/non-self-recognition raises a fundamental question for tumor immunology: how does the immune system discriminate emerging tumor cells from their normal counterparts? In this review article, we shall address the role of self/non-self-survey in the immune response to tumors, describe the mechanisms of immune surveillance against tumor cells, and the counter-mechanisms used by tumor cells to evade the immune response, and finally address the potential for chemoprevention of cancer in immunosuppressed individuals.

2. Tumor cells—the self/non-self-conundrum

Given that tumors arise from transformation of host cells, it is not surprising that some aspects of tumor immunity resemble autoimmunity. In keeping with the role of self/non-self-discrimination by antigen-reactive lymphocytes, tumor antigen-specific T cells commonly have lower affinity T cell receptors (TcR) for their antigenic ligands than would be expected of T cells specific for an exogenous agent [1–3]. In some cases, the ability of tumor antigen-derived epitopes to stimulate effective cytotoxic T lymphocyte (CTL) responses has been improved experimentally by the introduction of amino acid substitutions to the antigenic peptide ("altered peptide ligands") that either stabilise peptide-major histocompatibility complex (MHC) binding or peptide-MHC/TcR complex interaction [2–4]. However, T cell clones with high affinity for tumor antigenic peptides have been identified in melanoma patients which, on expansion in vitro and adoptive transfer, migrated to the tumor site and mediated antigen-specific immune responses [5]. Therefore, antigen affinity is not the only reason for lack of effective tumor immunity in vivo.

One of the surprises of tumor immunology was the finding that much of the adaptive immune response to tumor cells was directed against non-mutated self-proteins rather than against sites of mutation in self-proteins that differentiated them from normal sequence (reviewed in [6]). Indeed, some of these target antigens turned out to be proteins that were expressed in normal tissues, as well as in their tumor counterparts. This finding further emphasised the relationship between tumor immunity and autoimmunity. A clinical corollary of this interesting relationship is the relatively common finding of vitiligo in patients with melanoma responding to immunotherapy of their tumor.

However, there are fundamental differences between tumor cells and their normal counterparts that give the immune system a window of opportunity for discriminating tumor cells from normal tissues. One molecular hallmark of carcinogenesis is genetic instability, giving rise to mutations in self-proteins, chromosomal translocations (e.g. *bcr*/*abl* in chronic myeloid leukemia and other leukemias), overexpression of normal proteins (e.g. Her-2/neu) and expression of self-proteins not expressed in normal somatic cells (e.g. cancer-testis antigens). Each of these mutations gives the potential for self-proteins to be presented to the immune system in a manner more akin to the expression and presentation of non-self-antigens. These can be further classified as unique