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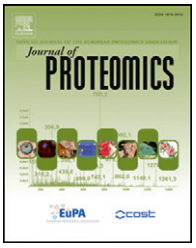

Review

Assessment of the humoral immune response to cancer☆

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ABSTRACT

One of the deadly hallmarks of cancer is its ability to prosper within the constraints of the host immune system. Recent advances in immunoproteomics and high-throughput technologies have lead to profiling of the antibody repertoire in cancer patients. This in turn has lead to the identification of tumour associated antigens/autoantibodies. Autoantibodies are extremely attractive and promising biomarker entities, however there has been relatively little discussion on how to interpret the humoral immune response. It may be that autoantibody profiles hold the key to ultimately uncovering neoplastic associated pathways and through the process of immunosculpting the tumour may have yielded an immune response in the early stages of malignant tumour development. The aim of this review is to discuss the utility of the autoantibody response that is elicited as a result of malignancy and discuss the advantages and limitations of autoantibody profiling. This article is part of a Special Issue entitled: Translational Proteomics.

Contents

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1. Immune system and cancer

The robustness of the immune response plays a vital role in maintaining health. The immune system is composed of a variety of interdependent defence mechanisms that collectively defend the body from external agents such as bacterial, parasitic, fungal and viral infections as well as internal processes such as the growth of tumour cells. Inappropriate immune responses can be detrimental as seen in autoimmune disease. However, much evidence now suggests that, in addition to the immune response recognising and preventing the development of cancer, the immune system can interact to promote and direct tumour growth [1,2]. The stages and mechanisms of how cancer and the immune system interact have been termed Immunosurveillance. Immunoselection (also termed Immunoediting) is a theory of immune interaction that is particularly interesting in terms of autoantibody profiling, immunosurveillance is divided into three phases, known as the 'three E's', Elimination, Equilibrium and Escape and Immunosubversion [3,4]. The interplay between the immune system and pre-cancerous and cancer cells is a vital part of further understanding the cancer–host relationship. In this review, we discuss how humoral immune system profiling of the antibody repertoire may hold promise in detecting early stages malignant processes. Improved and focussed studies to progress understanding of these processes could potentially uncover biomarkers for blood or tissue based diagnosis and imaging or potentially targets for treatment.

1.1. *Immunosurveillance*

Surveillance by the immune system is a process by which the host immune system (innate and adaptive) actively surveys the body from within. Immunosurveillance describes the process whereby the immune system recognises pre-cancerous cells and proposes that the immune system can identify and destroy cancer precursors in most cases [5]. For example, an important active component in tumour immunosurveillance has been shown to be the receptor Natural killer group 2, member D (NKG2D) [6-9]. NKG2D is a stimulatory receptor expressed on the surface of Natural Killer (NK) cells and on subsets of T-cells [10]. NKG2D ligands are generally absent from normal cell populations but are widely expressed on a variety of cancer cell lines and primary solid tumours such as colon cancer [11] and ovarian cancer [12]. Such ligands assist immune recognition resulting in clearance of transformed cells. NKG2D-deficient mice have been shown to be defective in tumour surveillance. These mice have also provided genetic evidence for surveillance of spontaneous tumour development by the NKG2D receptor [13]. Immunosurveillance and the immune system's interaction and destruction of pre-cancerous cells is very important in maintenance of health and prevention of tumour progression.

1.2. *Immunoselection*

The theory of immunoselection (also termed immunoediting) renders poorly immunogenic tumour cell variants that are 'primed' to evade the host's individual immune system. The role of immunoselection determines the robustness of the tumour for continual survival and growth within an immunocompetent environment [3]. Immunoselection is an extension of the immunosurveillance hypotheses and it has been proposed that tumour immunoselection encompasses three phases, termed the 'three E's' of cancer immunoselection; 1. Elimination. 2. Equilibrium. 3. Escape [4]. These stages are believed to have important functions in directing malignancy in an evolutionary manner [14–16].

Immunoselection is difficult to study directly in human cancers but there is evidence in support of this process. It

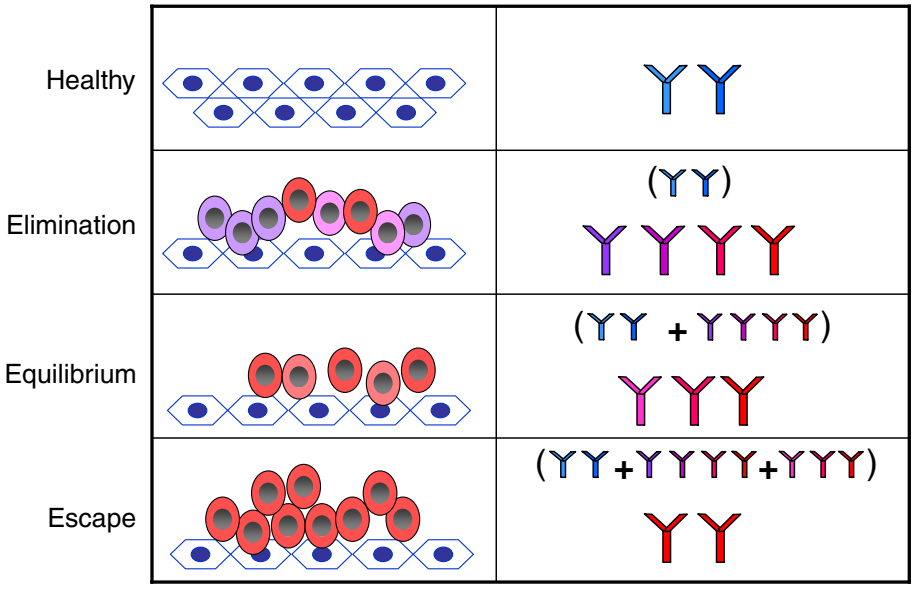

Fig. 1 – This figure proposes the development of the autoantibody response to cancer in relation to the 'three E's' of immunoselection. It is likely that the antibody profile determined after the escape phase will be an accumulation of previous stages. The 'cumulative profile' is denoted in brackets and is attributed to previous stages.