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Review

Autoantibody production in cancer—The humoral immune response toward autologous antigens in cancer patients

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ABSTRACT

A link between autoimmune responses and cancer via autoantibodies was first described in the 1950s. Since autoantibodies have been studied for their potential use as cancer biomarkers, the exact causes of their production remain to be elucidated. This review summarizes current theories of the causes of autoantibody production in cancer, namely, (1) defects in tolerance and inflammation, (2) changes in protein expression levels, (3) altered protein structure, and (4) cellular death mechanisms. We also highlight the need for further research into this field to improve our understanding of autoantibodies as biomarkers for cancer development and progression.

Contents

Abbreviations: dsDNA, double-stranded DNA; MIF, macrophage migration inhibitory factor; Ang-2, angiopoietin 2; CENPF, centromere protein F; Her2/neu, human epidermal growth factor receptor 2; MUC1, mucin 1; IMP2, insulin-like growth factor mRNA-binding family member 2; AORF, alternative open reading frame; CTAG1B/NY-ESO-1, cancer testis antigen 1B; OGFr, opioid growth factor receptor; PSA, prostate-specific antigen; TNF, tumor necrosis factor; MAGEA3, melanoma antigen A3; PASD1, cancer antigen containing the PAS domain 1; TGFβ, transforming growth factor beta; NKG2D, natural killer group 2 member D; ERp5, disulphide isomerase; MICA, MHC class 1 chain-related protein A; CTLA4, cytotoxic T lymphocyte associated protein 4; ATP, adenosine triphosphate; HMGB1, high mobility group B box protein 1.

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1. Introduction

The production of autoantibodies (AAbs) is believed to reflect greater immunologic reactivity in cancer patients and enhanced immune surveillance for cancer cells [1]. Since tumors originate from autologous cells containing self-antigens, it has been suggested that it is the abnormal exposure or presentation of these antigens that facilitates an autoimmune response [2].

Over the last few decades, AAbs have become of particular interest as cancer biomarkers as they can be easily extracted from serum via minimally invasive blood collection. Moreover, they exhibit increased levels in very early cancer stages [3] and are observed in patients with several carcinomas, including breast [4], lung [5], gastrointestinal [3], ovarian [6], and prostate [7]. What is more, their production may precede clinical confirmation of a tumor by several months or years [8]. Notably, one of the first historical reports of anti-tumor protein p53 (p53) antibodies indicated that the AAbs were detectable as early as 17–47 months prior to clinical tumor manifestation in uranium workers at high risk of lung cancer development [9]. Detection of AAbs has also been reported during the transition to malignancy [10]. Furthermore, AAbs may be valuable biomarkers as they are stable serological proteins [11] with high levels in serum despite low levels of the corresponding antigen [12]. Additionally, they persist for extended periods after the corresponding antigen is no longer detectable [6], at lasting concentrations and with long half-lives in blood, due to limited proteolysis and clearance from the circulation [13], making sample handling less arduous.

Studies have focused primarily on identifying AAbs as biomarkers rather than investigating the underlying causes of their production. However, the latter may reveal clues to the mechanisms involved rendering autologous proteins immunogenic. Such studies could not only lead to the development of novel biomarker assays, but also to the identification of novel therapeutic targets.

At present, the existence of a specific anti-tumor immune response, referred to as “cancer immunome,” indicates that tumors express antigens that are recognized as foreign by the host [11]. In the early stages of carcinogenesis, this immune response is thought to occur as a result of immune surveillance, the process by which the immune system recognizes and destroys autologous cells that have become cancerous [2,11]. In fact, histological examination of tumor affected tissues revealed the presence of large populations of tissue resident and circulating T and B cells that participate actively in immune surveillance [14].

As part of this surveillance, antigen presenting cells (APCs), i.e., dendritic cells, B cells, and macrophages, engulf, lyse, and present tumor-associated antigens (TAAs) on their cell surface for recognition by CD4 + helper T cells. Interaction between the APC and T helper cell triggers the APC release of cytokine and chemokine signals, resulting in T cell activation and proliferation. B cells with high affinity for a specific TAA encounter the antigen, engulf, lyse, and also display it on their cell surface for recognition and binding by activated T helper cells [15]. Lymphocyte recirculation into secondary lymphoid organs and peripheral tissue sites enhances this process, maximizing the frequency of transformed cell TAAs encountering naïve B cells. The binding of activated T cells to B cells displayed that TAAs initiate further release of cytokines and chemokines leading to B cell proliferation. A vast number of B lymphocytes primed against the same antigen are produced, some of which will serve as memory cells and others as effector cells that differentiate into antibody producing plasma cells responsible for the systemic release of the appropriate antibody [16]. Antibody–TAA binding thus represents the end stage of the humoral mechanism capable of initiating the destruction of transformed cells containing the corresponding antigen by, for example, labeling them (via opsonization) for faster macrophage recognition and phagocytosis. Direct binding of antibodies to the antigen can also block receptors associated with tumor cell proliferation and survival and AAbs can drive antigen uptake via dendritic cell Fc gamma receptors, leading to antigen cross-presentation and vigorous CD4 + and CD8 + T cell responses, complement dependent cytotoxicity, and natural killer cell-mediated antibody-dependent cellular cytotoxicity [17].

It is interesting to note that prolonged inflammation and the subsequent tissue destruction associated with autoimmune diseases [18] share many parallels with the humoral immune response to TAAs [19]. In fact, a repertoire of autoantibodies is shared by autoimmune conditions and cancer [20]. For example, 30% of all cancer patients have circulating anti-nuclear antibodies (ANAs) in their sera [21], autoantibodies associated with Sjögren's syndrome, systemic sclerosis, and systemic lupus erythematosus (SLE), while these are generally absent or present at very low levels in healthy individuals [22].

The exact factors that contribute to an enhancement or disturbance of immune surveillance leading to the production of autoantibodies in cancer are however still illusive, and the question remains as to how and why cellular components may be rendered immunogenic in cancer. Here we summarize some of the major theories surrounding the production of autoantibodies in cancer (Fig. 1), including loss of tolerance, inflammation, and changes in antigen expression, as well as their altered exposure or altered presentation, reduced degradation, post-translational modifications (PTMs), and their aberrant location or altered structure.

2. Tolerance defects and inflammation

2.1. tolerance defects

Approximately half of the lymphocyte population present in generative lymphoid organs is capable of binding to autoantigens [20]. In order to eliminate self-reactive lymphocytes entering the general circulation, all immature lymphocytes must undergo a series of checkpoints with processes aimed at maintaining central tolerance (tolerance to self). Lymphocytes will only mature successfully if they are non-reactive to autologous antigens and possess functional polypeptide chains necessary to build a functional pre-antigen receptor, pre-BCR, and pre-TCR for B and T cells, respectively. Self-reactive lymphocytes are either eliminated, by negative selection via clonal deletion facilitated apoptosis [23] or converted into a non-reactive state of clonal anergy [24]. Alternatively, they may be preserved by positive selection,

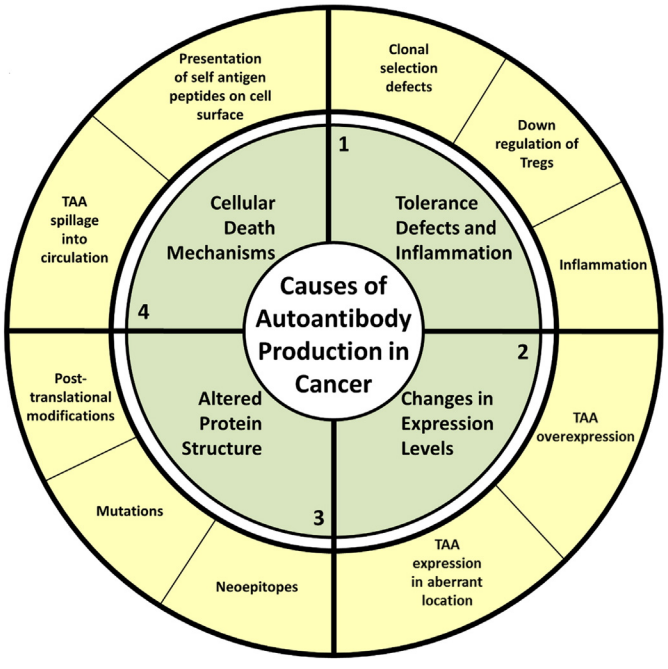

Fig. 1. Proposed causes of autoantibody production in cancer.

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