

2016

Autoantibody Production in Cancer—The Humoral Immune Response toward Autologous Antigens in Cancer Patients

Pauline Zaenker

Edith Cowan University, paulinez@our.ecu.edu.au

Elin Solomonovna Gray

Edith Cowan University, e.gray@ecu.edu.au

Melanie Ruth Ziman

Edith Cowan University, m.ziman@ecu.edu.au

[10.1016/j.autrev.2016.01.017](https://ro.ecu.edu.au/ecuworkspost2013/1968)

Originally published as: Zaenker, P., Gray, E. S., & Ziman, M. R. (2016). Autoantibody Production in Cancer—The Humoral Immune Response toward Autologous Antigens in Cancer Patients. *Autoimmunity reviews*, 15(5), 477-483. Original article available [here](#)

This Journal Article is posted at Research Online.

<https://ro.ecu.edu.au/ecuworkspost2013/1968>



Review

Autoantibody Production in Cancer—The Humoral Immune Response toward Autologous Antigens in Cancer Patients



P. Zaenker^{a,*}, E.S. Gray^a, M.R. Ziman^{a,b}

^a School of Medical and Health Sciences, Edith Cowan University, Joondalup, Perth, WA, Australia

^b Department of Pathology and Laboratory Medicine, The University of Western Australia, Crawley, Perth, WA, Australia

ARTICLE INFO

Article history:

Received 18 January 2016

Accepted 23 January 2016

Available online 28 January 2016

Keywords:

Autoantibody

Autoantibody production

Biomarker

Cancer

Immune surveillance

Humoral immune response

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, however 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.

© 2016 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Contents

1. Introduction	478
2. Tolerance defects and inflammation	478
2.1. Tolerance defects	478
2.2. Downregulation of regulatory T cells	479
2.3. Inflammation	479
3. Changes in protein expression levels	480
3.1. Overexpression of the corresponding antigen	480
3.2. Aberrant expression site of the corresponding antigen	480
4. Altered protein structure	480
4.1. Neopeptide exposure	480
4.2. Mutations	480
4.3. Post-translational modifications	480
5. Cell death mechanisms cause aberrant release of intracellular antigens	481
6. Concluding remarks and future perspectives	481
Conflict of interest	482
Financial disclosure statement	482
Take-home messages	482
References	482

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; OGF α , opioid growth factor receptor; PSA, prostate-specific antigen; TNF, tumor necrosis factor; MAGEA3, melanoma antigen A3; PASD1, cancer antigen containing the PAS domain 1; TGF β , 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.

* Corresponding author at: Edith Cowan University, 270 Joondalup Drive, Joondalup, Perth, WA 6027, Australia. Tel.: +61 8 63045716.

E-mail address: p.zaenker@ecu.edu.au (P. Zaenker).

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 cell displayed TAAs initiates 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,

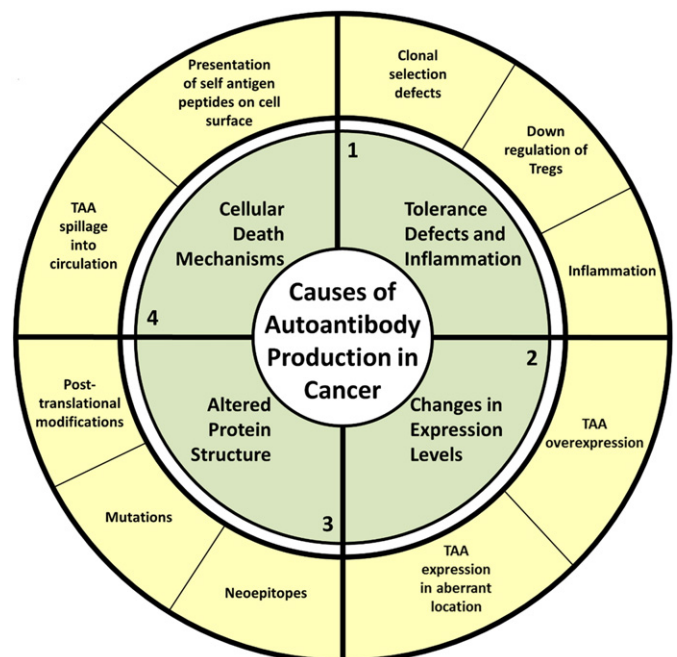


Fig. 1. Proposed causes of autoantibody production in cancer.

provided their antigen receptor alteration is induced, also known as receptor editing or revision [25]. Self-reactive B cells that have escaped primary developmental checkpoints are further controlled by additional peripheral checkpoints such as germinal center arrest [26]. However, the processes of maintaining central tolerance are complex and subject to error. For example, maintenance of clonal anergy is problematic as it requires constant receptor occupancy and signalling, and is easily reversed by dissociation of the corresponding self-antigen, resulting in anergic self-reactive B cells regaining responsiveness and potentially leading to the production of autoantibodies [27]. It is also believed that inappropriate survival of auto reactive lymphocytes by escape from clonal deletion results when their corresponding antigen is expressed at levels not high enough to induce clonal deletion [15,16].

Additionally, autoantibodies generated against autologous nuclear antigens are frequently found in cancer patient sera. Nuclear antigens are structurally disordered and their intrinsic proteolytic instability has been suggested to interfere with the binding efficiency to major histocompatibility complex (MHC) class II receptors throughout the elimination of self-reactive lymphocytes, enabling their escape from the primary lymphoid organs. Exposure of some autologous nuclear antigens to the immune system, i.e., following tumor cell lysis, may therefore result in the production of autoantibodies [28].

2.2. Downregulation of regulatory T cells

High titers of AAbs have been associated with regulatory T cell (Treg) downregulation. In fact, delayed tumor growth due to a reduction of Tregs has been correlated with an increase in effector T helper cells, germinal center B cells, and high titers of autoantibodies [29], such as anti-double-stranded DNA (dsDNA), ANAs, macrophage migration inhibitory factor (MIF), and angiopoietin 2 (Ang-2) antibodies, indicating a robust anti-tumor response in conjunction with cell-mediated immune response mechanisms [30].

In a recent study, Alvarez Arias et al. [30] utilized Qa-1 (HLA-E in humans) knock-in B6 Qa-1 D227 mice that harbor a point mutation in the MHC class Ib molecule, capable of impairing binding of CD8+ Treg subsets to the T cell receptor (TCR) leading to impairment of the Treg

suppressive activity. B6-DK mice were inoculated with B16 melanoma cells engineered to express the “B16-OVA” ovalbumin transgene. Increased titers of anti-OVA antibodies and substantially delayed tumor growth were observed in transgenic mice compared to wild-type control mice. Furthermore, passive transfer of antibodies from the treated B6-DK mice into a new cohort of mice highlighted that these autoantibodies could curtail tumor growth, with 60% of these mice remaining tumor free. By contrast, mice treated with autoantibodies from B6 wild-type mice developed tumors over time [30]. Thus, the downregulation of Tregs and an imbalanced CD8+ Treg/T helper cell ratio in favor of the effector T helper cells appeared responsible for the increase in protective autoantibody production (Fig. 2) in this model [30]. It may be possible that the reduced production of Tregs or similar Treg downregulatory mechanisms exist in human melanoma or other cancers, rendering Treg/TCR binding ineffective and promoting autoantibody production in some cancer patients, with potential beneficial outcomes.

2.3. Inflammation

Autoimmune responses, such as the production of autoantibodies, may be part of a chronic inflammatory response toward cancer cells and are associated with an array of immunological pathways, including the release of several cytokines discussed in later sections. Inflammation may be maintained throughout the duration of the cancer and increases the permeability of the nearby vasculature, thereby enabling easier access of immune cells to the site of the malignancy [30].

An induction of inflammation in the tumor microenvironment has been suggested to facilitate the release of intracellular antigens resulting in abnormal exposure of autologous antigens to the immune system, which may provide an explanation for the vast number of autoantibodies produced against intracellular antigens in cancer patients [28]. The tumor inflammatory microenvironment has therefore, along with changes in expression patterns of corresponding antigens, been regarded as one of the main causes of autoantibody production in cancer patients [31].

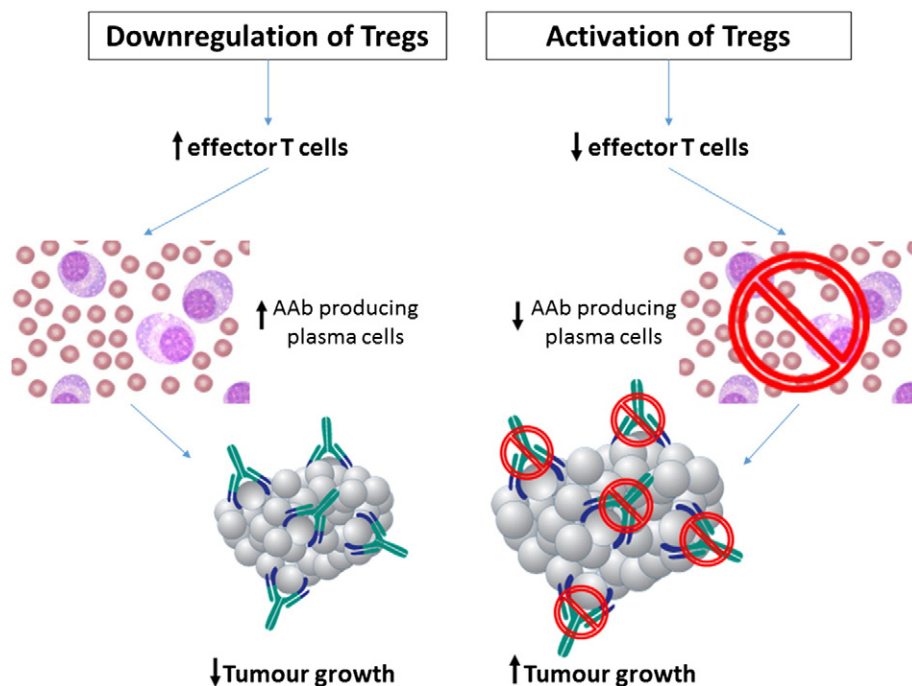


Fig. 2. Downregulation of Tregs correlates with high titers of autoantibodies and delayed tumor growth.

3. Changes in protein expression levels

3.1. Overexpression of the corresponding antigen

Most TAAs are non-mutated antigens that are produced at low levels in healthy cells and overexpressed during tumorigenesis, thus causing immunogenicity presumably by presentation of their antigenic peptides on human leukocyte antigen (HLA) class I molecules, at levels high enough to exceed the engaged TCR threshold required for CD4+ T cell activation, and thereby indirectly leading to antibody production against these autologous antigens [32].

A recent study by Hong et al. [33] suggested that increased anti-centromere protein F (CENPF) autoantibody levels, detected in a cohort of hepatocellular carcinoma patients, were likely produced in response to the overexpression of the protein in these cancer cells. Similarly, a strong correlation exists between human epidermal growth factor receptor 2 (Her2/neu) overexpression, detectable in 30% of adenocarcinomas [34], and the frequency of anti-Her2/neu antibodies found in breast cancer patients [35]. Goodell et al. [35] reported no autoantibody occurrence in breast cancer cases with low Her2/neu expression and 82% antibody occurrence in cases with high target protein expression levels.

Mucin 1 (MUC1) is an integral membrane protein whose expression is normally confined to the apical surface of breast ductal epithelium, a site that is relatively isolated from the immune system. MUC1 overexpression is detectable in 90% of all adenocarcinomas and is associated with increased aggressiveness of the tumor [36]. MUC1 autoantibodies, commonly detected in breast adenocarcinoma patients, are thought to be produced in response to overexpression of this target antigen [36]. Interestingly, the binding of antibodies to MUC1 is suggested to have an inhibiting effect on tumor invasive functions [37].

In early-stage ovarian cancer, p53-specific antibodies are produced due to the presence of mutant p53 in these tumors [38]. A recent study by Anderson et al. [6], compared p53-specific autoantibody production in patients with serous ovarian cancer to patients with non-serous ovarian cancer type and found that in the latter cases, p53 antibodies were still detectable but at much lower levels than in those with serous ovarian cancer, consistent with the lower frequency of p53 mutations in non-serous tumors [39]. Studies have demonstrated that the half-life of mutant p53 is markedly increased to several hours while the wild-type p53 displays a half-life of only a few minutes, resulting in aberrant accumulation of mutated p53 in the cell nucleus. Notably, immunogenic epitopes have been mapped primarily to both the N- and C-terminal portions of p53, but not to the central portion of the molecule which harbors the mutations, suggesting that the accumulation of the protein rather than the mutations per se may result in the generation of anti-p53 autoantibodies [40].

3.2. Aberrant expression site of the corresponding antigen

Autoantibody production in cancer patients may also be due to expression of the protein in an aberrant location.

Cancer testis (CT) expression is normally confined to distinct and immune privileged locations within the body, such as the gametes of the testis or ovaries and in trophoblasts of the placenta [41]. Their aberrant expression in somatic tissues has been associated with spontaneous autoantibody production in patients with various cancer types [42].

Similarly, autoantibody production against the oncofetal antigen insulin-like growth factor mRNA-binding family member 2 (IMP2) has been detected in the sera of 21% of hepatocellular carcinoma patients but is not detectable in patients with precursor conditions such as liver cirrhosis and chronic hepatitis. Oncofetal antigens are expressed throughout prenatal development and cease expression in all tissues shortly after birth, whereas their re-expression in adulthood has been associated with malignant transformation. This abnormal re-expression has been suggested to be the cause of autoantibody production in hepatocellular carcinoma patients [43].

4. Altered protein structure

4.1. Neoepitope exposure

It has been observed that autoantibodies are largely raised against intracellular self-antigens [28] that may be aberrantly expressed in cancer cells resulting in abnormal presentation of reactive neoepitopes to the immune system [44]. A neoepitope may be created by somatic mutations that change the protein structure or an epitope normally located within an unexposed region of the protein, may become exposed by a conformational change or stereochemical alteration of the protein structure, thus stimulating an immune response [45]. Furthermore, genetic instability, a hallmark of carcinogenesis [46], results in expression of neoantigens (containing neoepitopes) in tumor cells that in turn initiates an immune response against the tumor or the surrounding autologous tissue [47].

Certain structural motifs of antigens, including carbohydrate side chains, multivalency, epitope repetition, highly charged cell surfaces and coiled coils, have been found to enhance antigenicity [48]. Interestingly, autoantibodies elicited as a result of modified proteins are often able to bind to both the modified and unmodified form of the protein, possibly due to the gradual expansion of the spectrum of specificities recognized in B and/or T cell immune responses, also referred to as epitope spreading [49].

Furthermore, naturally occurring and cancer-associated molecular mimicry represented by the attachment of mimotopes, macromolecules such as peptides that mimic the structure of an epitope onto an APC, may also elicit a humoral immune response since the antibody for a given epitope will equally recognize the mimotope [3].

4.2. Mutations

All cancers carry somatic mutations which vary in frequency depending on the cancer type and its cause [50]. p53 is commonly mutated in a variety of cancers [51]. Altered p53 proteins produced from missense mutations may have acquired neo-antigenic determinants that stimulate antibody production [2,52]. Interestingly, despite the strong autoantibody specificity toward mutated p53, only 20–40% of patients with cancers harboring p53 missense mutations have p53 autoantibodies in their sera, indicating that other causes, such as protein accumulation as mentioned previously and HLA polymorphisms, must exist for autoantibody production to be facilitated in patients [40].

Notably, while missense point mutations leading to altered protein products are highly correlated with production of autoantibodies, stop, splice, and frameshift mutations do not generally appear to cause autoantibody production in lung cancer [53]. By contrast, immunological responses to antigens altered by frameshift mutations, have been detected in colorectal cancer patients [54].

Furthermore, the translation of mRNA from an alternative open reading frame (AORF) can lead to the generation of proteins bearing immunogenic determinants that can trigger humoral immune responses in cancer patients. For example, antigenic peptides encoded from the AORF of cancer-testis antigen 1B (CTAG1B), also known as NY-ESO-1, have been shown to elicit immunological responses in cancer patients [55]. Moreover, antibodies to the opioid growth factor receptor (OGFr) protein recognize an alternative-reading frame of the molecule in patients suffering from melanoma, prostate cancer, lung cancer, breast, and ovarian cancer [56].

4.3. Post-translational modifications

Post-translational modifications of proteins such as glycosylation, methylation, phosphorylation, sumoylation, citrullination, adenosine diphosphate-ribosylation, ubiquitination, and acetylation [57] are known to occur aberrantly in cancer, creating a vast diversity of modified proteins and greatly expanding the number of targets for cancer-

specific autoantibody production [13]. In fact, over 140 unique amino acid derivatives are produced as a result of post-translational modifications, which can be enzyme-mediated or spontaneous and can generate a neoepitope or enhance self-epitope presentation, inducing an immune response [44,57].

The most common cancer-related changes involve glycosylation [58] and phosphorylation [59], which can affect antigen processing, binding, and interaction of the MHC presented antigen with the TCR, therefore activating the T helper response needed to mount a humoral autoantibody response. Aberrant glycosylation, for example, has been observed in many cancers, causing the presentation of modified epitopes as TAAs that can override tolerance and induce antibody production in cancer patients. Tarp et al. [60] reported the presence of immunodominant epitopes on glycosyl moieties of mucin 1, which induce a humoral immune response in mucin-transgenic mice. Antibodies recognizing specific MUC1 O-glycopeptides have been detected in ovarian, breast, and prostate cancer patients [61], but MUC1 glycopeptides are also detectable at similar frequencies in healthy cancer-free controls and are therefore not cancer specific [62].

5. Cell death mechanisms cause aberrant release of intracellular antigens

How exactly the processing and metabolism of proteins can lead to the mounting of an autoimmune response in cancer patients has yet to be determined. Some studies have suggested that the cleavage of known nuclear and cytoplasmic proteins during apoptosis and/or accumulation due to insufficient clearance of secondary necrotic cells may play a role [39,63,64]. The ongoing destruction of tumor cells, throughout tumor development and progression, is thought to arise as a result of extensive cell proliferation and cell survival producing overwhelming cellular stresses [63], including ongoing immunological attacks, altered protein structures, genomic instability, DNA damage, altered transcriptional networks, and signal transduction, hypoxia as well as deprivation of nutrients [64]. Cell lysis following tumor cell necrosis and autophagy results in the spillage of autologous intracellular tumor contents into the blood, exposing cancer-specific, cancer-associated, or neoantigens to the immune system and effectively triggering an immune response and the production of autoantibodies [20,65,66]. For example, the release of prostate-specific antigen (PSA) into the serum of patients with malignant prostate tumors arises from cell lysis due to a disruption in the tissues between the prostate gland lumen and its capillaries, leading to anti-PSA antibody production [67].

Tumor cell lysis may also be promoted through secretion of cytokines, such as tumor necrosis factor (TNF) and interferon- γ , by T helper cells. TNF is an agent that causes tumor cell death by inducing thrombosis in tumor blood vessels, resulting in high levels of interferon-sensitive tumors releasing large numbers of cellular antigens, thereby triggering the production of multiple autoantibodies [68]. In a case study of one patient with hepatocellular carcinoma following radiation therapy, increases in TNF α were observed [69]. In another case study of a melanoma patient, increased melanoma antigen A3 (MAGEA3) autoantibody levels as well as autoantibodies against cancer antigen containing the PAS domain 1 (PASD1) were reported to be present in the patients sera following intracranial stereotactic radiosurgery and the commencement of Ipilimumab treatment [70]. In both case studies, the authors observed additional clearance of non-irradiated tumors, better known as the abscopal effect, after localized radiation therapy to the main lesion. Both the abscopal effect and an observed rise in autoantibody levels was suggested to be due to tumor antigen release and cytokine production upon cell death caused by irradiation of the tumor [69,70].

Furthermore, macrophages, and dendritic cells release immune suppressive mediators such as transforming growth factor beta (TGF- β) and interleukin-10 (IL-10), following their capture of apoptotic cells, thereby stimulating Tregs [71]. The capture of necrotic cells on the

other hand, activates effector immune responses, including the humoral response, by initiating the release of pro-inflammatory cytokines such as IL-1 β , IL-6, IL-12, and IL-23, capable of attenuating the effects of TGF- β and IL-10 [72]. Since cancer cells involve both apoptotic and necrotic cell death concurrently, the immune system is faced with opposing signals of immune tolerance and immune effector responses, and as a result, neither process gains full control.

The presentation of TAAs on the surface of dying tumor cells may be responsible for directing the immune response toward an activated effector response state thereby promoting autoantibody production (Fig. 3).

Cells that have natural killer group 2 member D (NKG2D) ligands presented on their cell surface, signal the presence of DNA damage within the cell and thus become detectable by surveillance immune cells [73]. In order to avoid recognition by the immune system, tumor cells shed, mediated by disulphide isomerase (ERp5) [74], the MHC class 1 chain-related protein A (MICA) protein leading to the downregulation of NKG2D ligands on the cell surface [75]. An interesting study by Jinushi et al. [76] showed that patients on granulocyte macrophage colony-stimulating factor-secreting tumor cell vaccines or cytotoxic T lymphocyte associated protein 4 (CTLA-4) immunotherapy, generated high titers of ERp5 and MICA antibodies and the production of these autoantibodies not only restored the immunologic cytotoxic attack against tumor cells due to the maintenance of NKG2D ligands on the cancer cell surface but also promoted cross-presentation of ingested tumor antigens by ACPs, thereby further strengthening the immunological anti-tumor attack. The release of additional danger signals such as adenosine triphosphate (ATP) and high mobility group B box protein 1 (HMGB1) from cancer cells undergoing autophagy may further aid in tipping the scales toward an effector immune response including AAb production [65].

Apoptotic cancer cells have also been found to present altered cleavage products and post-translationally modified self-proteins on surface blebs which promote autoimmunity [77]. Additionally, regulatory defects in apoptosis resulting in the maintenance of mutant/defective cells may render these autologous cells immunogenic.

6. Concluding remarks and future perspectives

AAb levels are detectable many months prior to the clinical manifestation of a tumor, persist for an extended period after removal of the corresponding antigen bearing tumor and in many ways reflect the overall immunogenicity and immune response toward the tumor.

To provide useful insights on the interplay between the humoral immune response and cancer, future studies should seek to investigate the causes of the production of AAb biomarkers. The exact mechanisms responsible for cancer-related autoantibody production are still largely unknown. As reviewed here, to date, several theories have been proposed which include 1) tolerance defects and inflammation, 2) changes in expression levels, 3) altered protein structure, as well as 4) cellular death mechanisms. It appears that it is the abnormal expression and/or alteration in the structure of the corresponding antigen that is most accountable for an immune response. However, failure of tolerance mechanisms, inflammation, and cell death affect the context in which the antigens are presented to the immune system, initiating the production of AAbs, in concert with other immune responses against transformed cancer cells. Due to the heterogeneity of cancer cells and the varied genetic and epigenetic differences between individual cancer patients, it is likely that anti-cancer humoral autoimmune responses originate from an array of such causes.

Furthermore, whether an increase or decrease in AAbs is beneficial to the overall patient survival is still controversial and seems to differ with each AAb. For instance, increases in AAb levels may be associated with complete tumor remission in some anti-cancer therapies [70]. While an increase of NY-ESO-1 autoantibodies has been shown to reflect increases in tumor burden in several cancers [78], decreases in AAb levels are observed with cancer progression in some cases. The cancer progression associated drop in AAb levels has been suggested to be due to “cancer

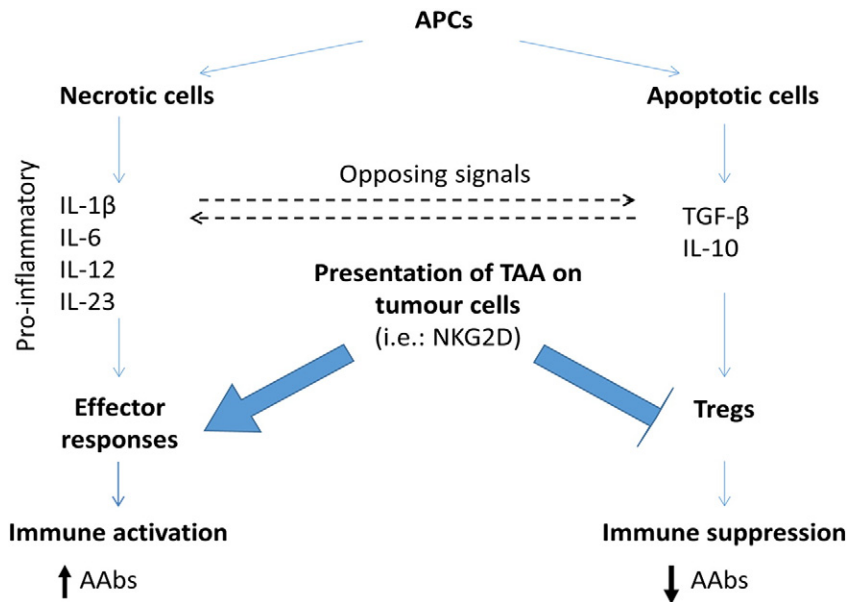


Fig. 3. The presentation of TAAs on the tumor cell surface directs the immune response toward autoantibody production.

immunoediting,” comprised of three phases, namely, elimination, equilibrium, and the escape phase, resulting in the survival of resistant, immune tolerant metastatic cancer cells [79]. AAb levels may therefore aid in monitoring the immune response when assessing the efficacy of existing and novel therapeutic agents and may prove effective in disease staging or as a predictor of recurrences and a favorable clinical outcome.

Finally, the presence of some autoantibodies has been correlated with indolent tumor growth and increased patient survival [80]. Therefore, understanding the causes of AAb production in different cancers may lead to the development of novel therapeutic agents or the timely application of existing treatments.

Conflict of interest

The authors of the manuscript declare no conflict of interest.

Financial disclosure statement

The author PZ receives ongoing financial support as part of an Inspiring Minds scholarship at Edith Cowan University while the other authors did not receive any additional financial support for this manuscript.

Take-home messages

- A repertoire of AABs is shared by autoimmune disorders and cancer.
- The causes of cancer-related AAB production remain yet to be elucidated.
- Tolerance defects, inflammation, and cell death affect TAA immune presentation.
- Abnormal TAA expression and structure appear most accountable for AAB production.
- AABs may be useful diagnostic, prognostic, and surveillance cancer biomarkers.

References

- [1] Kaae J, Wohlfahrt J, Boyd HA, Wulf HC, Biggar RJ, Melbye M. The impact of autoimmune diseases on the incidence and prognosis of cutaneous malignant melanoma. *Cancer Epidemiol Biomarkers Prev* 2007;16:1840–4.
- [2] Pardoll D. Does the immune system see tumors as foreign or self? *Annu Rev Immunol* 2003;21:807–39.
- [3] Zayakin P, Ancāns G, Siliņa K, Meistere I, Kalņina Z, Andrejeva SD, et al. Tumor-associated autoantibody signature for the early detection of gastric cancer. *Int J Cancer* 2013;132:137–47.
- [4] Anderson KS, Sibani S, Wallstrom G. Protein microarray signature of autoantibody biomarkers for the early detection of breast cancer. *J Proteome Res* 2011;10:85–96.
- [5] Chapman CJ, Thorpe AJ, Murray A. Immunobiomarkers in small cell lung cancer: potential early cancer signals. *Clin Cancer Res* 2010;17:1474–80.
- [6] Anderson KS, Cramer DW, Sibani S, Wallstrom G, Wong J, Park J, et al. Autoantibody signature for the serologic detection of ovarian cancer. *J Proteome Res* 2015;14:578–86.
- [7] Wang X, Yu J, Sreekumar A, Varambally S, Shen R, Giachero D. Autoantibody signatures in prostate cancer. *N Engl J Med* 2005;353:1224–35.
- [8] Caron M, Choquet-Kastylevsky G, Joubert-Caron R. Cancer immunomics: using autoantibody signatures for biomarker discovery. *Mol Cell Proteomics* 2007;6:1115–22.
- [9] Royahem J, Conrad K, Frey M, Melhom J, Frank KH. Autoantibodies Predictive Parameters of Tumor Development. Berlin: Pabst; 1988.
- [10] Zhang JY, Tan EM. Autoantibodies to tumor-associated antigens as diagnostic biomarkers in hepatocellular carcinoma and other solid tumors. *Expert Rev Mol Diagn* 2010;10:321–8.
- [11] Anderson KS, LaBaer J. The sentinel within: exploiting the immune system for cancer biomarkers. *J Proteome Res* 2005;4:1123–33.
- [12] Lu H, Goodell V, Disis ML. Humoral immunity directed against tumor-associated antigens as potential biomarkers for the early diagnosis of cancer. *J Proteome Res* 2008;7:1388–94.
- [13] Pedersen JW, Wandall HH. Autoantibodies as biomarkers in cancer. *Labmedicine* 2011;42:623–8.
- [14] Linnebacher M, Maletzki C. Tumor-infiltrating B cells. *Oncoimmunology* 2012;1:1186–8.
- [15] Goodnow CC, Sprent J, Fazekas de Groth B, Vinuesa CG. Cellular and genetic mechanisms of self tolerance and autoimmunity. *Nature* 2005;435:590–7.
- [16] Wardemann H, Nussenzweig MC. B-cell self-tolerance in humans. *Adv Immunol* 2007;95:83–110.
- [17] Carter P. Improving the efficacy of antibody-based cancer therapies. *Nat Rev Cancer* 2001;1:118–29.
- [18] Kamradt T, Mitchison NA. Tolerance and autoimmunity. *N Engl J Med* 2001;344:655–64.
- [19] Preiss S, Kammertoens T, Lambert C. Tumor-induced antibodies resemble the response to tissue damage. *Int J Cancer* 2005;115:456–62.
- [20] Bei R, Masuelli L, Palumbo C, Modesti M, Modesti A. A common repertoire of autoantibodies is shared by cancer and autoimmune disease patients: inflammation in their induction and impact on tumor growth. *Cancer Lett* 2009;281:8–23.
- [21] Torchilin VP, Lakoubov LZ, Estov Z. Antinuclear autoantibodies as potential antineoplastic agents. *Trends Immunol* 2001;22:424–7.
- [22] Fernández-Madrid F, Karvonen RL, Ensley J, Kraut M, Granda JL, Alansari H, et al. Spectra of antinuclear antibodies in patients with squamous cell carcinoma of the lung and of the head and neck. *Cancer Detect Prev* 2005;29:59–65.
- [23] Venanzi ES, Benoist C, Mathis D. Good riddance: thymocyte clonal deletion prevents autoimmunity. *Curr Opin Immunol* 2004;16:197–202.
- [24] Gauld SB, Merrell KT, Cambier JC. Silencing autoreactive B cells by anergy: a fresh perspective. *Curr Opin Immunol* 2006;18:292–7.
- [25] Gay D, Saunders T, Camper S, Weigert M. Receptor editing: an approach by autoreactive B cells to escape tolerance. *J Exp Med* 1993;177:999–1008.
- [26] Paul E, Lutz J, Erikson J, Carroll MC. Germinal center checkpoints in B cell tolerance in 3H9 transgenic mice. *Int Immunol* 2004;16:377–84.

- [27] Ding C, Yan J. Regulation of autoreactive B cells: checkpoints and activation. *Arch Immunol Ther Exp (Warsz)* 2007;55:83–9.
- [28] Carl PL, Temple BR, Cohen PL. Most nuclear systemic autoantigens are extremely disordered proteins: implications for the etiology of systemic autoimmunity. *Arthritis Res Ther* 2005;7:1360–74.
- [29] Kim HJ, Verbinen B, Tang X, Lu L, Cantor H. Inhibition of follicular T helper cells by CD8 + Treg is essential for self tolerance. *Nature* 2010;467:328–32.
- [30] Alvarez Arias DA, Kim H-J, Zhou P, Holderried TAW, Wang X, Dranoff G, et al. Enhanced murine antitumor immunity after genetic disruption of CD8 + regulatory T-cell activity. *Cancer Immunol Res* 2014;2:207–16.
- [31] Nanda NK, Sercarz EE. Induction of anti-self-immunity to scure cancer. *Cell* 1995;82:13–7.
- [32] Watanabe N, Arase H, Onodera M, Ohashi PS, Saito T. The quantity of TCR signal determines positive selection and lineage commitment of T cells. *J Immunol* 2000;165:6252–61.
- [33] Hong Y, Zhang B, Jia JD, Huang J. Identification of autoantibody based serological marker for early diagnosis of hepatocellular carcinoma by serological proteome analysis combined with protein microarray. *Hepatology* 2013;58(Suppl. 1).
- [34] Menard S, Casalini P, Campiglio M. Role of HER2/neu in tumor progression and therapy. *Cell Mol Life Sci* 2004;61:2965–78.
- [35] Goodell V, Waisman J, Salazar JG. Level of HER-2/neu protein expression in breast cancer may affect the development of endogenous HER-2/neu-specific immunity. *Mol Cancer Ther* 2008;7:449–54.
- [36] Yonezawa S, Goto M, Yamanda N. Expression profiles of MUC1, MUC2, and MUC4 mucins in human neoplasms and their relationship with biological behaviour. *Proteomics* 2008;8:3329–41.
- [37] Agrawal B, Krantz MJ, Reddish MA. Cancer-associated MUC1 mucin inhibits human T-cell proliferation, which is reversible by IL-2. *Nat Med* 1998;4:43–9.
- [38] Goodell V, Salazar LG, Urban N, Drescher CW, Gray H, Swensen RE, et al. Antibody immunity to the p53 oncogenic protein is a prognostic indicator in ovarian cancer. *J Clin Oncol* 2006;24:762–8.
- [39] Anderson KS, Wong J, Vitonis A, Crum CP, Sluss PM, LaBaer J, et al. p53 autoantibodies as potential detection and prognostic biomarkers in serous ovarian cancer. *Cancer Epidemiol Biomarkers Prev* 2010;19:859–68.
- [40] Soussi T. p53 antibodies in the sera of patients with various types of cancer: a review. *Cancer Res* 2000;60:1777–88.
- [41] Scanlan MJ, Gure AO, Old LJ. Cancer/testis antigens: an expanding family of targets for cancer immunotherapy. *Immunol Rev* 2002;188:22–32.
- [42] Simpson AJG, Caballero OL, Jungbluth A. Cancer/testis antigens, gametogenesis and cancer. *Nat Rev Cancer* 2005;5:615–26.
- [43] Zhang JY, Chan EK, Peng XX, Tan EM. A novel cytoplasmic protein with RNA-binding motifs is an autoantigen in human hepatocellular carcinoma. *J Exp Med* 1999;189:1101–10.
- [44] Hanash S. Harnessing immunity for cancer marker discovery. *Nat Biotechnol* 2003;21:37–8.
- [45] Genovese F, Karsdal MA, Leeming DJ, Liu T, Wang X. Molecular serum markers of liver fibrosis. *Biomark Insights* 2012;105.
- [46] Fearon ER, Vogelstein BA. Genetic model for colorectal tumorigenesis. *Cell* 1990;61:759–67.
- [47] Joseph CG, Darrah E, Shah AA, Skora AD, Casciola-Rosen LA, Wigley FM, et al. Association of autoimmune disease scleroderma with an immunologic response to cancer. *Science* 2014;343:152.
- [48] Plotz PH. The autoantibody repertoire: searching for order. *Nat Rev Immunol* 2003;3:73–8.
- [49] James JA, Harley JB. B-cell epitope spreading in autoimmunity. *Immunol Rev* 1998;164:185–200.
- [50] Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SAJR, Behjati S, Biankin AV, et al. Signatures of mutational processes in human cancer. *Nature* 2013;500:415–21.
- [51] Kandoth C, McLellan MD, Vandin F, Ye K, Niu B, Lu C, et al. Mutational landscape and significance across 12 major cancer types. *Nature* 2013;502:333–9.
- [52] Winter SF, Minna JD, Johnson BE, Takahashi T, Gazdar AF, Carbone DP. Development of antibodies against p53 in lung cancer patients appears to be dependent on the type of p53 mutation. *Cancer Res* 1992;52:4168–74.
- [53] Reuschenbach M, von Knebel Doeberitz M, Wentzensen N. A systematic review of humoral immune responses against tumor antigens. *Cancer Immunol Immunother* 2009;58:1535–44.
- [54] Schwitalle Y, Kloor M, Eiermann S, Linnebacher M, Kienle P, Knaebel HP, et al. Immune response against frameshift-induced neopeptides in HNPCC patients and healthy HNPCC mutation carriers. *Gastroenterology* 2008;134:988–97.
- [55] Wang RF, Johnston SL, Zeng G, Topalian SL, Schwartzentruber DJ, Rosenberg SA. A breast and melanoma-shared tumor antigen: T cell responses to anti-genic peptides translated from different open reading frames. *J Immunol* 1998;161:3598–606.
- [56] Mollick JA, FS Hodi, RJ Soiffer, LM Nadler, Dranoff G. MUC1-like tandem repeat proteins are broadly immunogenic in cancer patients. *Cancer Immunol* 2003;3:3.
- [57] Anderton SM. Post-translational modifications of self-antigens: implications for autoimmunity. *Curr Opin Immunol* 2004;16.
- [58] Hakomori S. Glycosylation defining cancer malignancy: new wine in an old bottle. *Proc Natl Acad Sci USA* 2002;99:10231–3.
- [59] Blume-Jensen P, Hunter T. Oncogenic kinase signalling. *Nature* 2001;411.
- [60] Tarp MA, Sorensen AL, Mandel U, Paulsen H, Burchell J, Taylor-Papadimitriou J, et al. Identification of a novel cancer-specific immunodominant glycopeptide epitope in the MUC1 tandem repeat. *Glycobiology* 2007;17:197–209.
- [61] Wandall HH, Blixt O, Tarp MA. Cancer biomarkers defined by autoantibody signatures to aberrant O-glycopeptide epitopes. *Cancer Res* 2010;70:1306–13.
- [62] Burford B, Genty-Maharaj A, Graham R. Autoantibodies to MUC1 glycopeptides cannot be used as a screening assay for early detection of breast, ovarian, lung or pancreatic cancer. *Br J Cancer* 2013;108:2045–55.
- [63] Edinger AL, Thompson CB. Death by design: apoptosis, necrosis and autophagy. *Curr Opin Cell Biol* 2004;16:663–9.
- [64] Vogelstein B, Kinzler KW. Cancer genes and the pathways they control. *Nat Med* 2004;10:789–99.
- [65] Peter C, Wesselborg S, Herrmann M, Lauber K. Dangerous attraction: phagocyte recruitment and danger signals of apoptotic and necrotic cells. *Apoptosis* 2010;15:1007–28.
- [66] Tan EM, Zhang J. Autoantibodies to tumor-associated antigens: reporters from the immune system. *Immunol Rev* 2008;222:328.
- [67] Pan D, McCahy P. Patient knowledge about prostate-specific antigen (PSA) and prostate cancer in Australia. Warragul, Victoria: Department of Urology, Casey Hospital, Berwick and West Gippsland Health Service; 2011.
- [68] de Visser KE, Eichten A, Coussens LM. Paradoxical roles of the immune system during cancer development. *Nat Rev Cancer* 2006;6:24–37.
- [69] Ohba K, Omagari K, Nakamura T. Abscopal regression of hepatocellular carcinoma after radiotherapy for bone metastasis. *Gut* 1998;43:575–7.
- [70] Stamell EF, Wolchok JD, Gnjatic S, Lee NY, Brownell I. The abscopal effect associated with a systemic anti-melanoma immune response. *Int J Radiat Oncol Biol Phys* 2013;85:293–5.
- [71] Jinushi M, Nakazaki Y, Dougan M, Carrasco DR, Mihm M, Dranoff G. MFG-E8 mediated uptake of apoptotic cells by APCs links the pro- and anti-inflammatory activities of GM-CSF. *J Clin Invest* 2007;117:1902–13.
- [72] Rock KL, Kono H. The inflammatory response to cell death. *Annu Rev Pathol* 2007.
- [73] Gasser S, Orsulic S, Brown EJ, Raulat DH. The DNA damage pathway regulates innate immune system ligands of the NKG2D receptor. *Nature* 2005;436:1186–90.
- [74] Kaiser BK, Yim D, Chow IT. Disulphide-isomerase-enabled shedding of tumour-associated NKG2D ligands. *Nature* 2007;447:482–6.
- [75] Groh V, Wu J, Yee C, Spies T. Tumour-derived soluble MIC ligands impair expression of NKG2D and T-cell activation. *Nature* 2002;419:734–8.
- [76] Jinushi M, Hodi FS, Dranoff G. Therapy-induced antibodies to MHC class I chain-related protein A antagonize immune suppression and stimulate antitumor cytotoxicity. *Proc Natl Acad Sci U S A* 2006;103:9190–5.
- [77] Doyle HA, Mamula MJ. Post-translational protein modifications in antigen recognition and autoimmunity. *Trends Immunol* 2001;22:443–9.
- [78] Barrow C, Browning J, MacGregor D. Tumor antigen expression in melanoma varies according to antigen and stage. *Clin Cancer Res* 2006;12:764–71.
- [79] Schreiber RD, Old LJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science* 2011;331:1565–70.
- [80] Graus F, Dalmau J, Rene R, Tora M, Malats N, Verschuuren JJ, et al. Anti-Hu antibodies in patients with small-cell lung cancer: association with complete response to therapy and improved survival. *Clin Oncol* 1997;15:2866–72.