Published in final edited form as:

Cancer Immunol Immunother. 2009 October ; 58(10): 1535–1544. doi:10.1007/s00262-009-0733-4.

A systematic review of humoral immune responses against tumor antigens

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Abstract

This review summarizes studies on humoral immune responses against tumor associated antigens (TAA) with a focus on antibody frequencies and the potential diagnostic, prognostic, and etiologic relevance of antibodies against TAAs. We performed a systematic literature search in Medline and identified 3619 articles on humoral immune responses and TAAs. In 145 studies meeting the inclusion criteria, humoral immune responses in cancer patients have been analyzed against over 100 different TAAs. The most frequently analyzed antigens were p53, MUC1, NY-ESO-1, c-myc, survivin, p62, cyclin B1 and Her2/*neu*. Antibodies against these TAAs were detected in 0 to 69% (median 14%) of analyzed tumor patients. Antibody frequencies were generally very low in healthy individuals, with the exception of few TAAs, especially MUC1. For several TAAs, including p53, Her2/*neu*, and NY-ESO-1, higher antibody frequencies were reported when tumors expressed the respective TAA. Antibodies against MUC1 were associated with a favorable prognosis while antibodies against p53 were associated with poor disease outcome. These data suggest different functional roles of endogenous antibodies against TAAs. Although data on prediagnostic antibody levels is scarce and antibody frequencies for most TAAs are at levels precluding use in diagnostic assays for cancer early detection, there is some promising data on achieving higher sensitivity for cancer detection using panels of TAAs.

Keywords

Humoral immune response; autoantibodies; cancer; tumor antigens

Introduction

Under physiological conditions, auto-tolerance prevents reactions of the immune system directed against self-antigens. Disturbance of self-tolerance can lead to autoimmune diseases that are characterized by chronic inflammation and/or tissue destruction [1]. It is well established that immune responses against self-antigens can occur in cancer patients and although they may sometimes result in autoimmune-disease-like disorders (paraneoplastic syndromes), the initiation of these immune reactions is most likely different from primary autoimmune diseases. Apart from a loss of self-tolerance that is considered important for the development of autoimmune diseases, immune responses in cancer patients may be initiated by alterations in the tumor itself that result in increased immunogenicity of self-antigens [2].

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Several antigens have been identified that are expressed in tumor cells but not at all or only at very low levels in normal cells and might therefore function as tumor associated antigens capable of priming the immune system to recognize tumor cells [3,4].

An antigen-specific adaptive immune response may be composed of activated cytotoxic CD8 + T cells that are able to directly destroy antigen expressing target cells, different CD4+ T cell subsets that modulate the strength, duration, and efficacy of the immune reaction, and B cells that produce antigen specific antibodies (humoral immune response) [5].

Tumor associated antigens can emerge through different mechanisms, such as coding DNA mutations that lead to new epitopes in expressed proteins (e.g. p53), posttranslational modifications with immunological relevance (e.g. under-glycosylated MUC1), and altered tissue specific expression patterns or levels that can lead to the exposure of antigens usually expressed solely in immuno-privileged sites (e.g. NY-ESO-1) [6–8].

Spontaneous adaptive immune responses have been found against many tumor antigens in cancer patients [9,10]. The analysis of humoral immune responses against tumor antigens could yield diagnostic and prognostic markers and might lead to the exploration of new targets for immunotherapy. Our review summarizes the literature on humoral immune responses against tumor antigens with three major goals: 1. to summarize frequencies of antibodies against tumor antigens in patients with various cancer entities and healthy controls, 2. to summarize data on the diagnostic and prognostic impact of humoral immune responses against tumor antigens, and 3. to understand underlying biological mechanisms of humoral immune responses against tumor antigens and their potential relevance for cancer immunotherapy.

Currently, there are no standardized protocols or even certified assays to study humoral immune responses against tumor antigens. Likewise, there is no general agreement in which populations to study humoral immune responses against tumor antigens. Therefore, we have also put a strong focus on the technical aspects of measuring humoral immune responses with the goal to identify common sources of heterogeneity and to propose efforts to standardize these approaches.

Material and Methods

A systematic literature search was performed of studies published in Medline until June 30, 2008, using the keywords: (humoral immune response AND cancer), (humoral immune response AND tumor antigen), (autoantibodies AND tumor antigen). All studies that evaluated spontaneous humoral immune response against one or several tumor antigens in serum or plasma samples were included. In addition to papers identified in the primary search, reference lists of included articles were analyzed for additional manuscripts related to the topic. We only considered studies analyzing humoral immune responses against a-priori targets. Findings from proteomic analyses or tumor cDNA expression library based serological studies (e.g. SERPA, SEREX) were excluded unless the findings were confirmed in independent immunoassays. Antibody reactivities observed in vaccination studies and case reports about single patients were not considered.

We included studies analyzing sera or plasma samples from patients with invasive cancers, precancers, benign diseases and healthy controls. We included self-antigens that could be assigned to one of the above described categories of tumor antigens. Studies on antinuclear antibodies (ANA) or antibodies against onconeural and viral antigens were excluded. Since there is no standardized nomenclature for tumor antigen names we used the most common designation found in the literature. All antigen names were confirmed in the ExPASy database (<http://www.expasy.org>) to avoid using multiple antigen or protein names. Multiple protein names were only found for IMP3 (insulin-like growth factor II mRNA-binding protein 3),

which was also named Koc [11–13]. For MUC1, different epitope regions have been analyzed, including core peptide epitopes (often simply named MUC1) and carbohydrate glycan-epitopes (e.g. TF and Tn). MUC1 is the only protein for which we separately report the results for different epitopes. Similarly, only for MUC1, Ig subclasses were consistently reported and are presented separately in our analysis. For other antigens, Ig subclasses were not systematically reported.

We analyzed the studies for antibody frequencies and associations between antibody presence and tumor stage or course of the disease as well as for the used serological method. We calculated weighted antibody frequencies stratified by tumor site for each antigen. Some studies did not report antibody frequencies at a specified cut-off value. These studies could not be included in the weighted average calculation but were assessed for findings on associations between antibody presence and tumor stage or prognosis.

Results and Discussion

Prevalence of humoral immune responses against tumor antigens

The initial Medline search yielded 3619 abstracts using the above-described search terms. Of these, 145 studies were identified which reported spontaneous humoral immune responses against one or several self-tumor antigens according to the above described criteria (supplemental table 1).

Humoral immune responses in cancer patients have been found against a wide variety of cellular and extracellular proteins. In total, 107 different tumor antigens were investigated in 145 studies (included in supplemental table 1). Most of the antigens identified were derived from overexpressed or mutated proteins. 42.0% (45/107) were cytoplasmatic proteins, 26.1% (28/107) were expressed predominantly in the nucleus (transcription factors, cell cycle regulators), 21.4% (23/107) were membrane bound proteins (receptors, cell adhesion proteins) and 10.3% (11/107) were extracellular proteins (extracellular matrix proteins, secreted proteins).

Only 20 out of the 107 antigens were analyzed in more than 1 study, 8 in 5 or more studies and 3 in 10 or more studies. The antigens analyzed in 5 or more studies (by descending frequency) were p53 (37 studies, 17 tumor sites, 7764 tested samples, including controls), MUC1 core peptide (13 studies, 7 tumor sites, 2136 samples), NY-ESO-1 (13 studies, 11 tumor sites, 1528 samples), c-myc (9 studies, 7 tumor sites, 2968 samples), survivin (9 studies, 8 tumor sites, 2132 samples), p62 (6 studies, 11 tumor sites, 2773 samples), cyclin B1 (6 studies, 6 tumor sites, 2353 samples) and Her2/neu (5 studies, 3 tumor sites, 771 samples). Table 1 shows the weighted antibody frequencies for antigens analyzed in five or more studies for the most frequently analyzed tumor sites (breast, colorectal, liver and lung) as well as for healthy controls. For p53 antibodies, frequencies are also included for ovarian, esophageal and oral cancer, since in these cancers the highest p53 antibody frequencies have been demonstrated repeatedly. Antibodies were detected in 0 to 69% (median 14%) of analyzed tumor patients, while for most antigens, antibodies were rarely found in healthy controls (0–3%). The most evident exception is the MUC1 core peptide where antibodies could be found in 53.0% (IgM) and 23.3% (IgG) of healthy controls (weighted average frequencies). It has to be noted that several studies used the antibody levels in the control group to define their cutoffs which could result in an overall low level of reactivity in healthy controls. Weighted average frequencies of antibodies against all antigens analyzed in more than one study are shown for all analyzed tumor sites in supplemental table 2.

Methods used to measure humoral immune responses against tumor antigens

77.2% (112/145) of the studies on humoral immune responses against tumor antigens used ELISA assays, followed by western blotting (20.7%, 30/145 studies). Only 2.1% (3/145) of the studies used RIA or bead based multiplex serology. The antigens used as targets for the immunoassays were derived from recombinant proteins in 75.9% (110/145) of the studies, followed by cell line extracts (11.7%, 17/145 studies) and synthetic peptides (9.7%, 14/145 studies). Tumor extracts were used in 2.8% (4/145) of the studies to detect serum antibodies (supplemental table 1). Few studies validated their ELISA findings with an independent method, mostly using Western Blot or less frequently immunoprecipitation.

Most studies measured only IgG isotypes. For antibody responses against MUC1 epitopes, IgM antibodies were found more frequently than IgG in healthy controls, although the data are not completely consistent [14,15]. The reported association of humoral immune responses against MUC1 with survival benefit in cancer patients was associated with IgG rather than with IgM responses in most studies [16–18].

Even within a tumor site, a wide range of antibody frequencies against the same tumor antigen has been reported in different studies. p53 antibodies in esophageal cancer patients were found in 60.0% (36/60) of tested patients in one study, while a second study reports p53 antibodies in only 7.0% (5/71) of esophageal cancer patients [19,20]. Similarly, c-myc antibody frequency in hepatocellular carcinoma ranged from 1.3% (1/77) to 36.9% (24/65) [20,21]. In addition to different assays used, various methods of normalization and to define cutoffs have been applied. Frequently, both background reactivity and cut-off were determined based on reactivity against a negative control antigen such as recombinant constructs only consisting of the tag, e.g. histidine or GST without the target antigen sequence or against albumin only [22,23]. Other studies defined cutoffs by setting a threshold based on reactivity in normal control sera of various origins (e.g. threefold the standard deviation) [12,21]. While one can assume that the targeted epitope plays an important role in determining antibody frequencies, this has only been demonstrated for the different MUC1 epitopes [24].

Association between antigen expression and humoral immune responses

For some antigens a high correlation between antigen (over)-expression and frequencies of humoral immune responses was found. Most data exist for p53, where antibody prevalence was associated with p53 overexpression or p53 mutations that lead to subsequent extensive accumulation of the protein in the cell [25–32]. Similarly, NY-ESO-1 antibody frequency was higher in patients with NY-ESO-1 expressing tumors (up to 83%) as compared to patients with NY-ESO-1 negative tumors (no antibody response) [33–35]. Goodell et al. demonstrated a strong correlation between antibodies against Her2/neu and Her2/neu overexpression in breast cancer (82% antibodies in cases with strong expression versus no antibodies in cases with weak expression) [36]. The finding that antibodies against MUC1 frequently occur in healthy individuals has been related to benign conditions like inflammations that lead to expression of hypo-glycosylated immunogenic MUC1 epitopes [37]. Against other antigens, antibodies were not detectable or only at low frequencies despite a strong overexpression of the antigen (Melan A, p16^{INK4a}) [35,38]. The presence of antibodies in patients with antigen-negative tumors has been reported in some studies and could indicate either a loss of antigen-expression after immune priming and selection of antigen negative tumor cells or antigen expression in tissues that were not analyzed for expression, e.g. distant metastases [34,39].

Association between tumor stage and humoral immune responses

Antibodies against several tumor associated antigens such as p53, NY-ESO-1, survivin and tyrosinase were found more frequently in advanced tumor stages which corroborates the importance of antigen load and duration of antigen exposure for the induction of humoral

immune responses [39–43]. Higher incidence and titers of Her2/neu and MUC1 antibodies have been detected mainly at early stages [14,23,44,45] (Table 2, Supplemental table 3) although Her2/neu antigen expression is known to increase in advanced metastatic disease [46,47]. The loss of antibodies despite continued or even enhanced expression of the antigen may suggest that loss of antibodies leads to disease progression. However, these hypotheses have not been evaluated in prospective studies.

Diagnostic and prognostic relevance of humoral immune responses against tumor antigens

Several studies evaluated the use of humoral immune responses against tumor antigens as a serological biomarker for cancer. Antibodies against most tumor antigens are only found in 0–3% of healthy controls and seem to be highly specific for cancer, but average antibody frequencies against single antigens in tumor patients unselected for antigen expression rarely exceed 15% (table 1, supplemental table 2). Rare examples such as ECPKA and EpCAM have positivity rates of 70% or 90% in some cancer sites [48,49]. Therefore, a reasonable clinical sensitivity for a diagnostic test cannot be expected for currently tested antigens. Recent studies show evidence that measuring antibodies against a panel of specific antigens could increase sensitivity substantially [48,50–54].

Specific associations between humoral immune responses against tumor antigens and prognosis could impact clinical management and might suggest a functional role of the immune response in tumor biology. Studies that have reported associations of antibody presence with survival are shown in table 3 for the most frequent antigens and in supplemental table 4 for all antigens.

p53—p53 is mutated in over 50% of all cancers such as esophageal, lung, colorectal, and ovarian and humoral immune responses can be observed that correlate to accumulation of the mutated protein in the cell [32]. Poor survival of p53-antibody positive patients has been demonstrated in many studies for various tumor sites [19,31,55–64]. This association might reflect the higher antigen load in more advanced stages that have a worse prognosis. It has also been speculated that specific p53 mutations are associated with antibody production and that p53 antibodies might reflect specific mutations that lead to a more aggressive tumor [26,65]. Furthermore, two mechanisms explaining a tumor promoting role of p53 antibodies in tumor immunosurveillance have been described: Antibodies directed against p53 could inhibit antigen uptake by antigen presenting cells through the formation of immune complexes [66–68]. There is also evidence for an immune inhibitory effect of cytokines secreted by B cells that might result in suppression of effective cytotoxic T cell responses directed against p53 [69].

Only very few studies analyzed antibodies in individuals with a premalignant tumor stage and even less studies were designed prospectively to evaluate the risk of cancer development in antibody positive patients. Although antibodies against p53 could be found in patients with premalignant oral lesions and in heavy smokers with risk for development of lung cancer [55,70–72], the clinical utility of p53 antibody serology in monitoring high risk individuals needs to be evaluated in prospective studies. So far, there are only anecdotal reports of anti-p53 immune responses in a prospective setting [73–75].

For several tumor sites a decline or even disappearance of p53 antibody levels few weeks after surgical tumor removal has been demonstrated, which is in line with the hypothesis that constant stimulation of the immune system by the antigen is necessary to maintain high antibody levels [63,74,76,77]. Disappearance of NY-ESO-1 antibodies after tumor resection has also been demonstrated [33,78]. These findings led to the suggestion that antibody serology might be a tool for detection of disease recurrence. However, the predictive value of antibodies for tumor recurrence has not been demonstrated in prospective studies yet.

MUC1—The epithelial mucin MUC1 is overexpressed in over 90% of all adenocarcinomas, such as breast, colorectal, pancreatic and ovarian cancers and associated with an aggressive behavior of the tumor [79]. Altered glycosylation patterns of MUC1 may induce immune responses on the cellular and humoral level and tumor vaccines and monoclonal antibodies based on this antigen are tested in clinical trials [37]. The presence of MUC1 antibodies has been associated with improved survival in early stage patients with ovarian, gastric, lung, pancreatic or breast cancer [14,16–18,45,80–83]. It is difficult to demonstrate a causal relationship between antibody presence and longer survival, as the development of antibodies in longer survival patients may simply reflect protracted exposure to the antigen. Tumor immune surveillance is most likely significantly affected by cell mediated immunity, thus functional modulations cannot be attributed to humoral responses alone [84,85]. Increased expression of MUC1 in adenocarcinomas may affect cellular adhesion and metastasis by interfering with integrin- and cadherin-mediated adhesion [86]. Some data suggest a functional role of MUC1 antibodies by binding MUC1 proteins and inhibiting their tumor invasive functions [87]. MUC1 containing immune complexes are frequently found in cancer patients [88].

Hypoglycosylated MUC1 derivatives may also be generated by inflammations and other prevalent benign conditions in otherwise healthy individuals [37]. Since MUC1 antibodies are repeatedly found in healthy controls, it is conceivable that an immune response could be primed that confers a protective effect for the development of tumors. Cramer et al. showed a protective effect of humoral immune responses against MUC1 on the development of ovarian cancer [89].

Her2/neu—Her2/neu is overexpressed in 30% of all adenocarcinomas, such as breast, colorectal and ovarian cancers and associated with poor disease outcome [90]. The monoclonal recombinant anti-Her2/neu antibody Trastuzumab is successfully used to treat Her2/neu overexpressing breast cancers [91]. Interestingly, although no clinical effects in terms of survival benefit have been reported for endogenous Her2/neu antibodies, it has been shown that these antibodies can modulate the transforming properties of Her2/neu signaling towards an anti-proliferative state, similar to what has been demonstrated for the therapeutic Her2/neu antibody [92]. It can be speculated that the levels of spontaneously induced endogenous Her2/neu antibodies are insufficient to confer relevant growth inhibitory effects. In support of this hypothesis, high titers of endogenous Her2/neu antibodies induced by vaccination with peptides were shown to improve survival [91,93].

Conclusions and Perspective

Antibodies against tumor antigens are frequently found in the serum of cancer patients and have been analyzed in many studies during the last years. However the biological and clinical relevance of humoral immune responses against tumor antigens has not been systematically evaluated so far. Two questions are especially important when analyzing humoral immune responses against tumor antigens: 1) How are humoral immune responses against tumor antigens generated and how is tumor biology modulated by these immune responses? 2) Can antibodies against tumor antigens be used as serological biomarkers for cancer early detection, post-therapy surveillance or estimation of prognosis?

Overall, the mechanisms by which tumor proteins become immunogenic and induce humoral and/or cellular immune responses remain largely unknown. Both cellular and humoral immune responses have been found independently from each other and also against different epitopes. Based on the data summarized in this review, a common functional role of humoral immune responses against tumor antigens is very unlikely. Some antibodies directed against tumor associated antigens seem to be mere markers of exposure to the antigen without functional

relevance. These immune responses might be used for cancer early detection, prognosis, and post-treatment surveillance. Data on prediagnostic antibody levels is scarce so that it is currently unclear what the predictive value of prediagnostic humoral immune responses might be. Even in blood samples obtained at diagnosis, antibody frequencies for most tumor antigens are low precluding their use in diagnostic assays for cancer detection; however there is some promising data on achieving higher sensitivity of antibody serology for cancer detection using panels of tumor antigens. Also, by analyzing the antibody spectrum against tumor associated antigens, it might be possible to detect cancer subtypes with specific molecular and/or immunologic features that could be relevant for novel therapeutic approaches.

Humoral immune responses against p53 have been shown to be associated with poor prognosis. While this might be primarily related to increased exposure with the antigen, antibodies might also reflect p53 mutations that lead to a more aggressive tumor behavior. Also, it cannot be excluded that direct immune-modulatory mechanisms affect tumor biology. Associations of antibodies with favorable prognosis were repeatedly reported for MUC1 antibodies and may be related to interference of antibodies with MUC1-induced tumor growth promoting mechanisms. A similar cancer-suppressive mechanism has been suggested for endogenous antibodies directed against Her2/neu. Based on these observations, it may be suggested that cancer vaccines targeting these antigens should not only be designed to induce cytotoxic cellular immune responses, but also CD4 T cell and B cell responses.

Further studies using combination of antigens will be necessary to identify appropriate antigen panels and evaluate the suitability of antibody serology for diagnostic purposes. Additional efforts in this field should cover more systematically dynamic changes of antibody levels during the course of disease, especially associations with therapy response and survival. The functional role of humoral immune responses against tumor antigens needs to be further analyzed in the context of cellular immune responses and especially in cancer immunotherapy settings. Future data should be generated using more standardized methods, especially with respect to data normalization and threshold definition for antibody positivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Antibody frequencies in breast, colorectal, liver, lung cancer and healthy controls against antigens analyzed in five or more studies. For p53 antibodies, frequencies are also included for ovarian, esophageal and oral cancer. Protein function and cellular localization are from the ExPASy database (www.expasy.org)

antigen	function	localization	tumor site	n studies	samples analyzed	antibody frequency (%) (weighted average)	antibody frequency range (%)	references
c-myc	RNA splicing	nucleus, cytoplasm	breast	3	169	26.6	18.8–37.6	[12,20,21]
			liver	4	349	20.1	1.3–36.9	[12,13,20,21]
			lung	4	331	12.4	9.1–17.7	[12,20,94,95]
			colorectal healthy	3	154	11.7	4.4–15.4	[12,20,96]
				7	1017	1.0	0.0–3.4	[12,13,20,21,94–96]
cyclin B1	cell cycle control	cytoplasm, nucleus	lung	2	112	34.8	26.8–42.9	[12,21]
			colorectal	3	142	29.6	15.6–40.0	[12,21,96]
			liver	2	207	13.0	12.3–13.4	[12,13]
			breast healthy	1	64	4.7	-	[12]
				6	911	1.4	0.0–2.4	[12,13,21,96–98]
Her2/neu	growth factor receptor	membrane	breast	2	124	26.6	21.2–55.0	[36,99]
			lung	1	104	12.5	-	[94]
			healthy	2	150	2.0	2.0–2.0	[94,100]
MUC1 (IgG)	adhesion molecule	membrane	colorectal	1	56	48.2	-	[45]
			breast	2	154	42.9	40.4–44.1	[14,101]
			lung	1	104	34.6	-	[101]
			healthy	5	116	23.3	0.0–31.1	[14,23,45,94,102]
MUC1 (IgM)	adhesion molecule	membrane	healthy breast	2	230	53.0	42.5–62.9	[14,23]
				1	154	48.7	-	[14]
NY-ESO-1	unknown	cytoplasm	lung	3	303	18.2	4.2–22.0	[35,94,103]
			liver	2	281	8.9	2.2–12.2	[78,104]
			breast	1	26	7.7	-	[35]
			healthy colorectal	4	169	0.6	0.0–2.0	[34,35,94,104]
				1	25	0.0	-	[35]
p53	cell cycle control	nucleus, cytoplasm	ovarian	5	486	45.5	24.8–59.5	[55,56,64,76,105]
			esophageal	4	257	34.6	7.0–60.0	[20,22,63,83]
			oral	3	116	29.3	18.8–34.3	[19,106,107]
			liver	5	364	12.9	9.1–25.0	[11–13,20,108]
			breast	7	593	12.5	4.7–19.0	[12,20,26,57,61,109,110]
			lung	5	439	9.1	7.1–26.8	[12,20,59,94,110]
			colorectal	8	1643	7.7	1.3–23.8	[12,13,20,31,58,96,109,111]
			healthy	17	1136	2.0	0.0–6.3	[12,13,19,20,31,56,63,94,96,98,100,105,109,112–115]
p62	insulin like growth factor II mRNA binding protein	cytoplasm, membrane	lung	2	140	19.3	17.9–21.4	[12,13]
			liver	4	299	7.7	10.7–17.7	[12,13,116,117]
			healthy	5	554	0.7	0.0–3.1	[12,13,98,116,117]
			breast colorectal	2	162	0.0	5.1–7.8	[12,13]
				2	110	0.0	9.2–11.1	[12,13]
survivin	apoptosis inhibitor	cytoplasm, nucleus	lung	2	93	20.4	10.7–51.3	[12,118]

antigen	function	localization	tumor site	n studies	samples analyzed	antibody frequency (%) (weighted average)	antibody frequency range (%)	references
			breast	2	110	14.6	7.8–23.9	[12,119]
			liver	3	236	12.7	10.8–24.1	[12,13,120]
			colorectal	1	45	4.4	-	[12]
			healthy	6	538	0.7	0.0–2.5	[12,13,42,98,121,122]

Table 2

Studies reporting an association of humoral immune responses with tumor stage for tumor antigens analyzed in five or more studies

antigen	result	tumor site(s)	reference(s)
Her2/neu	higher antibody prevalence in early stages	breast	[44]
MUC1		breast, gastric, colorectal, ovarian	[14,23,45]
NY-ESO-1	higher antibody prevalence in advanced stages	esophageal	[39]
p53		colorectal, oral, gastric, breast, lymphoma, esophageal, ovarian	[19,31,58,60–64]
survivin		head and neck	[42]

Table 3

Studies reporting an association of humoral immune responses with prognosis for tumor antigens analyzed in five or more studies

antigen	results	tumor site(s)	reference(s)
MUC1	antibodies associated with survival benefit	breast, gastric, lung, ovarian, pancreatic	[14,16–18,23,82]
NY-ESO-1	antibodies associated with poor prognosis	prostate	[40]
p53		ovarian, breast, colorectal, lung	[55–59]