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The crossroads between cancer immunity and autoimmunity: antibodies to self antigens

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TABLE OF CONTENTS

1. ABSTRACT

The production of autoantibodies to self antigens is dependent on the failure of immune tolerance. Cancer cells express antigens which elicit a spontaneous immune response in cancer patients. The repertoire of autoantibodies found in cancer patients partly covers that of patients with autoimmune diseases. Biological activities of autoantibodies to self antigens may induce paraneoplastic syndromes which reflect the attempt of cancer patients to counteract tumor growth. Autoantibodies with similar specificities may have different effects in cancer and autoimmune disease patients due to different immunological microenvironments. Tregs dysfunction has been observed in patients with paraneoplastic syndromes and/or with autoimmune diseases, while the increase of Tregs has been associated with poor cancer patients prognosis. Novel therapies have employed antibodies against Tregs immune-checkpoint receptors with the aim to boost immune response in cancer patients. The presence of autoantibodies to tumors antigens has also been investigated as a marker for cancer detection and cancer patients prognosis. This report reviews the current knowledge on the analysis and meaning of autoantibodies to self antigens detected in cancer and autoimmune disease patients.

2. INTRODUCTION

The production of autoantibodies to self antigens is dependent on the breakdown or failure of immune tolerance mechanisms toward self-antigens. The immune system does not recognizes self-antigens in physiological conditions, but after the failure of immune tolerance these antigens may elicit T and B cells immune response (1). The immune response of autoreactive B cells occurs via central and peripheral tolerance mechanisms. During the central tolerance the autoreactive B cells are eliminated by receptor editing, that leads to rearrangement of light-chain Ig genes to generate a new B cell with non-self-reactive receptors. During peripheral tolerance, the autoreactive B cells are removed via several mechanisms, including inhibition mediated by FcγRIIb, clonal inhibition by the Siglec/SIaE pathway, inhibition by T regulatory cells (Tregs) in an MHC class II- and CD40L-dependent manner, clonal deletion and anergy

(1). In addition, during development autoreactive T cells are initially deleted by negative selection in thymus and then by peripheral tolerance through Tregs, clonal deletion and anergy (2). Thus, defective immune tolerance mechanisms affect autoimmunity by increasing the prevalence of autoreactive lymphocytes. Autoantibodies to self antigens are found both in sera from patients with systemic autoimmune diseases and with cancer (3, 4). However these autoantibodies display a different immunological background leading to different effects in cancer and autoimmune disease. The presence of serum autoantibodies to abnormally expressed tumor antigens might reflect the attempt of cancer patients to counteract cancer cells growth, while autoantibodies found in autoimmune disease are the result of breakdown of self-tolerance and induce pro-inflammatory responses and tissue injuries (5).

3. IMMUNE RESPONSE TO SELF ANTIGENS IN CANCER PATIENTS PARTLY COVERS THAT CHARACTERISTIC OF PATIENTS WITH AUTOIMMUNE DISEASES

Cancer cells express tumor antigens able to elicit a spontaneous immune response in cancer patients. Of note, the repertoire of autoantibodies found in cancer patients partly covers that characteristic of patients with autoimmune diseases (5). These autoantibodies might be useful as diagnostic or prognostic markers in cancer patients and as serological markers for the diagnosis of autoimmune diseases (6, 7). Table 1 reports examples of autoantibodies found both in cancer and autoimmune disease patients (5, 8-168).

Specific autoantibodies against nuclear antigens were detected both in cancer and in autoimmune disease patients. These autoantibodies recognized single- and double-stranded DNA, Ro/SS-A, La/SS-B, centromere, Jo-1, Smith antigens (Sm), small nuclear ribonucleoproteins (snRNP), topoisomerase I and II, nucleolar phosphoprotein B23/nucleophosmin, nucleolar organizer antigen NOR-90 and RNA polymerase III (5, 8-30). For example, anti-Ro/SS-A and anti-La/SS-B were prevalent in patients with Sjogren's syndrome (13) and systemic lupus erithematosus (SLE) (11) and in patients with hematological malignancies as well (5). Among the others, autoantibodies to p53, MDM-2, c-Myc and c-Myb were frequently detected in cancer and autoimmune disease patients. Autoantibodies against p53 were found in gastric, ovarian, colorectal, breast, head and neck cancer patients as well as in patients with SLE, rheumatoid arthritis (RA), dermatomyositis, autoimmune thyroiditis and hepatitis, primary biliary cirrhosis and systemic sclerosis (5, 31, 32). Autoimmune disease and cancer patients have also been found to exhibit autoantibodies against MDM-2, which is the p53 inhibitor (33, 34). Anti-c-Myc autoantibodies have been reported to occur in patients with gastric, breast, colon and ovarian cancer as well as in patients with SLE, Graves' disease, mixed connective tissue disease, dermatomyositis and autoimmune hemolytic anemia (5, 27, 34-39). Patients with colon, ovarian, breast and lung cancer as well as patients with SLE have been found to produce autoantibodies against the c-Myb protein (40). Both categories of patients generate autoantibodies against cyclin-B1, survivin, p16, 14-3-3 proteins, eukaryotic translation initiation factor 4G (eIF-4G) and RAF1 (14, 27, 28, 34-36, 40-48). Autoantibodies against the cyclic citrullinated peptide (CCP) were detected in patients with Sjogren's syndrome and psoriatic arthritis (51, 52) as well as in lymphoma patients (49). Anti-CCP antibodies are highly specific for RA and have recently been used in the clinical classification of this disease. These antibodies are more specific than rheumatoid factor (RF) for the diagnosis of RA (50). Furthermore, anti-RF antibodies are present in about 74% of patients with Sjogren's syndrome, in particular in the early stage of disease, and also in patients with autoimmune pancreatitis (13). Serum of patients with melanoma, bladder and gastrointestinal cancers contain anti-CCP autoantibodies as well (53, 54). Circulating autoantibodies against smooth muscle antigens (ASMA), including actin, troponin and tropomyosin, have been detected in patients with hepatocarcinoma, lung, breast, gastric, ovarian, melanoma, cervix, thymoma cancers, as well as in patients with Sjogren's syndrome, autoimmune hepatitis and pancreatitis, primary biliary cirrhosis and other autoimmune diseases (12, 19, 20, 55, 56, 58-62). The principal autoantibodies against the thyroid gland are anti-thyroid peroxidase (TPO), anti-thyroglobulin (TG) and anti-thyroid stimulating hormone receptor (TSH-R). Indeed, anti-TPO and anti-TG antibodies are mainly detected in patients with Hashimoto's thyroiditis, but they also occur in 70% of patients with Graves' disease (169). In addition, patients with diabetes, RA, systemic sclerosis, celiac disease, autoimmune gastritis, Sjogren syndrome as well as cancer patients with gastric MALT-type lymphoma, breast and thyroid cancer also display autoantibodies anti-TPO and anti-TG (5, 51, 63-73). Autoantibodies to extracellular matrix (ECM) components, including collagen, fibronectin and laminin, have been reported in RA, autoimmune thyroiditis, SLE, systemic sclerosis, Crohn's disease, primary Raynaud's disease, epidermolysis bullosa and pemphigo. Sera from patients with breast, prostate, lung and nasopharyngeal cancers displayed anti-ECM components autoantibodies (5, 11, 74-80). Autoimmune disease and cancer patients also exhibit autoantibodies against heat shock proteins (HSP), including HSP-60, -70, -90 and glucose-regulated protein 78 (GRP78). Autoantibodies against one or more HSPs have been found to occur in patients with SLE, RA, Sjogren's syndrome, mixed connective tissue diseases, diabetes, Behçet's disease, autoimmune retinopathy, encephalomyelitis and hepatitis, dermatitis herpetiformis and juvenile dermatomyositis, as well as

Table 1. Examples of autoantibodies to self antigens found both in patients with cancer and autoimmune disease.

Autoantibodies		Cancer site or histological subtype	Autoimmune disease	References
Anti-nuclear antigens	Anti-Dna	Hematological malignancies, lymphoma, ovary, HCC, stomach, colon-rectum	SLE, AIH-PBC overlap	5, 8-12
	Anti-Ro/SS-A	Lymphoma, hematological malignancies	SS, SLE, RA, PBC, dermatomyositis, SS-SLE overlap, systemic sclerosis	5, 8, 11, 13-15
	Anti-La/SS-B	Breast, lymphoma, SCLC, hematological malignancies	SS, SLE	5, 8, 11, 13
	Anti-CENP	Breast, SCLC, NHL, HCC	SS, SLE, RA, systemic sclerosis, PBC	5, 14, 16-19
	Anti-Jo-1	Stomach, lymphoma	SS, polymyositis	8, 20, 21
	Anti-Sm	Hematological malignancies, kidney, lymphoma, gastrointestinal, ovary	SLE, mixed connective tissue disease	5, 8, 11, 21
	Anti-U1 snRNP	Lung	SLE, mixed connective tissue disease	5, 11, 22
	Anti-U3 snRNP	HCC	Systemic sclerosis	5, 14
	Anti-Topoisomerase I (Scl-70)	Stomach, lymphoma	Systemic sclerosis, SLE, mixed connective tissue disease	8, 14, 20, 21
	Anti-Topoisomerase II	Breast, HCC	Juvenile RA, diabetes mellitus, SLE, localized scleroderma, systemic sclerosis, dermatomyositis	23-25
	Anti-B23/ Nucleophosmin	HCC, breast, prostate, ovary, pancreas, lung, colon	Systemic sclerosis, RA, SLE, scleroderma	5, 26-29
	Anti-NOR-90	HCC	Systemic sclerosis, Raynaud's syndrome, RA, SLE	5, 14
	Anti-RNA Polimerase III	Breast	Systemic sclerosis	14, 30
	Anti-p53	Stomach, ovary, colon-rectum, breast, esophagus, head and neck, HCC, bladder, lung, cervix, uterus, pancreas, lymphoma, biliary tract, hematological malignancies, prostate, glioma, skin	SLE, RA, dermatomyositis, AITD, AIH, PBC, AIH-PBC overlap, systemic sclerosis	5, 31, 32
	Anti-MDM2	Lung, prostate	SLE, systemic sclerosis	33, 34
	Anti-c-Myc	Stomach, lung, breast, colon, ovary, HCC, hematological malignancies, prostate	SLE, Graves' disease, mixed connective tissue disease, dermatomyositis, autoimmune hemolytic anemia	5, 27, 34-39
	Anti-c-Myb	Colon, ovary, breast, lung	SLE	40
Anti-Cyclin-B1		Lung, breast, HCC, prostate	SLE, systemic sclerosis	27, 34, 36, 40
Anti-Survivin		Stomach, ovary, pancreas, lung, colon, breast, HCC, prostate	SLE, systemic sclerosis	14, 28, 34, 35, 41
Anti-p16		Lung, breast, HCC, prostate	SLE, systemic sclerosis	27, 34, 36, 42
Anti-14-3-3 proteins		Lung, HCC, prostate	RA, SLE, systemic sclerosis	27, 34, 43, 44
Anti-eIF-4G		Prostate	RA	45, 46
Anti-RAF1		Colon-rectum	Autoimmune inner ear disease	47, 48
Anti-CCP		Diffuse large B-cell lymphoma	RA, SS, psoriatic arthritis	49-52
Anti-RF		Bladder, melanoma, gastrointestinal	SS, autoimmune pancreatitis, RA, SLE	11, 53-57
ASMA	Anti-Actin Anti-Troponin Anti-Tropomyosin	Stomach, HCC, melanoma, lung, breast, ovary, cervix, thymoma	SS, AIH, autoimmune pancreatitis, PBC, AIH-PBC overlap, celiac disease, primary sclerosing cholangitis	12, 19, 20, 55, 56, 58-62

Anti- Thyroid antigens	Anti-TPO	Gastric MALT-type lymphoma, breast, papillary thyroid	AITD, type 1 diabetes, RA, celiac disease, systemic sclerosis, autoimmune gastritis	5, 51, 63-68
	Anti-TG	DTC, papillary thyroid, gastric MALT-type lymphoma	AITD, type I diabetes, RA, SS, autoimmune gastritis	5, 69-73
Anti-ECM components	Anti-Collagen	Lung, prostate	RA, PV, SLE, epidermolysis bullosa, systemic sclerosis, Hashimoto's thyroiditis, Graves' disease, Chron's disease, Raynaud's disease	5, 74-78
	Anti-Fibronectin	Nasopharyngeal, prostate	RA, SLE, Hashimoto's thyroiditis	5, 74, 78
	Anti-Laminin	Breast, prostate	SLE, PV, systemic sclerosis, Raynaud's disease, Hashimoto's thyroiditis	11, 76, 78-80
Anti-HSPs	Anti-HSP60	HCC, breast, ovary, osteosarcoma, colon-rectum, gastric MALT-type lymphoma	Behçet disease, type 1 diabetes, SLE, RA, mixed connective tissue disease, autoimmune retinopathy, dermatitis herpetiformis, juvenile dermatomyositis, AIH	5, 17, 81-86
	Anti-HSP70	Breast, HCC, nasopharyngeal	Dermatitis herpetiformis, AIH	36, 84, 86-88
	Anti-HSP90	Ovary, multiple myeloma, cholangiocarcinoma, breast, osteosarcoma, prostate	Dermatitis herpetiformis, autoimmune encephalomyelitis, RA, SLE, autoimmune bullous diseases, type 1 diabetes, AIH	5, 28, 74, 79, 84, 86, 89-91
	Anti-GRP78	HCC, colon-rectum, prostate, ovary	RA, SLE, SS	28, 92-95
Anti-onconeural antigens	Anti-Hu (ANNA-1)	SCLC	Autoimmune limbic encephalopathy non paraneoplastic	96, 97
	Anti-Ri (ANNA-2)	SCLC, breast, ovary	Opsoclonus myoclonus syndrome	40, 98
Anti-enzymes	Anti-α-enolase	Lung, pancreatic ductal, breast, leukemia, head and neck, melanoma, esophagus	SLE, mixed connective tissue disease, systemic sclerosis, Behçet's disease, RA, Hashimoto's encephalopathy, celiac disease, AIH, PBC, primary sclerosing cholangitis	5, 99-105
	Anti-GAD	Lung, breast, thymoma	Type 1 diabetes, non-paraneoplastic limbic encephalitis, Stiff-person syndrome, cerebellar ataxia, Batten disease	60, 106-108
	Anti-Tyrosinase	Melanoma	Vitiligo	109
	Anti-Transglutaminase	Lymphoid malignancies	Celiac disease, autoimmune polyendocrine syndrome type 1, SS, type 1 diabetes	5, 110, 111
	Anti-CA II	Pancreas, melanoma	SS, SLE, RA, autoimmune pancreatitis, autoimmune retinopathies, type 1 diabetes, PBC, Graves' disease, systemic sclerosis, autoimmune endometriosis	55, 56, 112-120
	Anti-GAPDH	HCC	SLE	87, 121
	Anti-Peroxiredoxin	Prostate, breast, esophagus, lung, HCC	SLE, RA, Behçet's disease, vasculitis syndrome, systemic sclerosis	14, 36, 87, 122-126
	Anti-SOD	HCC, lung	RA, SLE	87, 127, 128
	Anti-Factor XIII	Lymphoid malignancies	Celiac disease, autoimmune haemorrha-philia, primary anti-phospholipid syndrome, RA	5, 129-131
Anti-Ribosomal P proteins		Head and neck, breast, prostate, colon-rectum	SLE, AIH, mixed connective tissue disease	11, 74, 132- 136
Anti-Mitochondrial antigens		Breast	PBC, SS, AIH, RA, SLE	11, 13, 73, 137, 138
Anti-Centrosome		Breast	RA, SLE, scleroderma	139

Anti-Receptors	Anti-Fas receptor	Colon	SLE, systemic sclerosis, silicosis	140, 141
	Anti-ER	Breast	SLE, systemic sclerosis	142, 143
	Anti-AChR	Thymoma	Myasthenia gravis	144, 145
Anti-VGCC		SCLC	Lambert-Eaton syndrome	40, 146
Anti-CD20		NHL, CLL	RA, SLE, SS	5, 147, 148
Anti-Annexin		Lung, colon-rectum, prostate, breast, ovary	Anti-phospholipid syndrome, SLE, RA, systemic sclerosis, connective tissue disease, autoimmune rheumatic disease, polymyositis	47, 122, 149-152
Anti-α-fetoprotein		HCC, colon-rectum	SLE, juvenile Batten disease	5, 17, 47, 153
Anti-Phospholipids		Breast, hematological malignancies, lung, colon-rectum, melanoma, kidney	RA, SLE, anti-phospholipid syndrome, systemic sclerosis, mixed connective tissue disease, Behçet's disease, systemic sclerosis, systemic vasculitis	5, 11, 154-159
Anti-Dsg-1/Dsg-3		NHL, chronic lymphocytic leukemia	PV	160, 161
Anti-Cytokeratin 8		Head and neck, breast, lung, cervix, bronchi, HCC	RA, AIH	162-165
Anti-IMP		HCC, breast, colon, prostate, ovary, stomach	SLE	17, 34-36, 166, 167
Anti-IFN-α		Thymoma	Autoimmune polyendocrinopathy syndrome type 1	5
Anti-α_2-HSG		Breast	Autoimmune endometriosis	120, 168

HCC: Hepatocellular carcinoma; SLE: Systemic lupus erithematosus; AIH: Autoimmune hepatitis; PBC: Primary biliary cirrhosis; RA: Rheumatoid arthritis; SS: Sjögren's syndrome; SCLC: Small cell lung cancer; CENP: Centromere nuclear protein; NHL: non-Hodgkin lymphoma; Jo-1: Istidil-tRNA sintetasi; Sm: Smith antigen; snRNP: small nuclear ribonucleoprotein; AITD: Autoimmune thyroid disease; eIF-4G: Eukaryotic translation initiation factor-4G; CCP: Cyclic citrullinated peptide; RF: Rheumatoid factor; ASMA: Anti-smooth muscle antibodies; TPO: Thyroid peroxidase; DTC: Disseminated tumor cells; TG: Thyroglobulin; PV: Pemphigus vulgaris; HSP: Heat shock protein; GRP78: Glucose-regulated protein 78; ANNA: Anti-neuronal nuclear antibody; GAD: Glutamic acid decarboxylase; CA II: Carbonic anhydrase II; GADPH: Glyceraldehyde 3-phosphate dehydrogenase; SOD: Superoxide dismutase; ER: Estrogen receptor; AchR: Acetylcholine receptor; VGCC: Voltage-gated calcium channels; CD20: B-lymphocyte antigen CD20; CLL: Chronic lymphocytic leukemia; Dsg: Desmoglein; IMP: Insulin-like growth factor II mRNA-binding protein; IFN: Interferon; α_2-HSG: α_2-Heremans Schmid-glycoprotein.

in patients with osteosarcoma, HCC, breast, ovarian and other types of cancer (5, 17, 28, 36, 74, 79, 81-95). Autoantibodies against onconeural antigens, like Hu (ANNA-1) and Ri (ANNA-2) and against enzymes, like α-enolase, glutamate decarboxylase (GAD), tyrosinase, transglutaminase, carbonic anhydrase II (CAII), glyceraldehyde 3-phosphate dehydrogenase (GAPDH), peroxiredoxin, superoxide dismutase (SOD) and coagulation factor XIII, have been reported in both patients with autoimmune diseases and cancer (5, 14, 36, 40, 55, 56, 60, 87, 96-131). Circulating autoantibodies against the ribosomal P proteins (P0, P1 and P2) are directed mainly to the carboxy-terminal epitope common to all three proteins and have been identified for the first time in SLE patients. Patients with autoimmune hepatitis and mixed connective tissue diseases display these antibodies too. We have recently demonstrated the presence of autoantibodies against P proteins in head and neck, breast, prostate and colorectal cancer patients (11, 74, 132-136). Patients with autoimmune diseases and cancer also exhibit autoantibodies against mitochondrion and centrosome antigens (11, 13, 73, 137-139). In addition, the presence of autoantibodies against several membrane receptors, including Fas receptor, estrogen receptor (ER) and acetylcholine receptor (AchR) has been reported in sera of patients with various autoimmune diseases and with cancer (140-145). Anti-voltage-gated calcium channel (VGCC), anti-CD20, anti-annexin, anti-α-fetoprotein, anti-phospholipid, anti-desmoglein (DSG), anti-cytokeratin-8, anti-insulin-like growth factor II mRNA-binding proteins (IMP), anti-interferon (IFN)-α and anti-α_2-HSG (Heremans Schmid-glycoprotein) autoantibodies have also been found in sera from patients with cancer and autoimmune disease (5, 11, 17, 34-36, 40, 47, 120, 122, 146-168).

4. FEATURES OF SELF ANTIGENS INVOLVED IN THE AUTOREACTIVE IMMUNE RESPONSE: IMMUNOLOGICAL PROPERTIES AND ABNORMAL EXPRESSION

The events inducing the generation of autoantibodies recognizing common antigens in cancer and autoimmune disease patients are still not completely clear. However, some theories have been proposed. Plotz described that the features of self antigens that might induce the production of autoantibodies can be related to: a) their structural properties; b) their catabolism and fate after cell death;

c) their concentration and type of microenvironment; d) their immunological/pro-inflammatory properties (170).

Among the structural properties, the binding of a self antigen to nucleic acid or the presence of a highly charged surface, or repetitive surface elements, or a coiled-coil in a self antigen might promote autoreactive immune response (170). Other observations suggested that the removal of death cells could induce the production of antibodies to self antigens. Necrosis is commonly considered as a pro-inflammatory and immunogenic type of death, which furnishes “danger signals” able to activate the innate immune response and then the adaptive immunity (171, 172). Indeed, self antigens are expressed on the surface of apoptotic or necrotic cells or, are modified by cell-death-mediated protein proteolysis or by molecules cleavage as occurs for nucleic acid antigens (170). The presence of cleavage sites for caspases, Granzyme B or cathepsins in autoantigens may lead to presentation of cryptic epitopes capable of stimulating autoreactive T and B lymphocytes (170, 173).

Another important issue is related to changes in autoantigen cancer cells expression. The overexpression or the expression in aberrant place of a given self antigen could induce immune responses in cancer patients. In addition, autoantibodies generation may also be due to an altered protein structure. Neoepitopes exposure, mutations and post-translational antigens modifications, such as glycosylation, methylation, phosphorylation, sumoylation, citrullination, adenosine diphosphate-ribosylation, ubiquitination, and acetylation, can overcome self tolerance mechanisms. In particular, post-translational modifications can influence the recognition of self antigen by the immune system, by affecting antigen processing, by binding and interaction of the MHC with the T cell receptor (TCR) (3). Targeting neoepitopes/neoantigens is a new therapeutic strategy for cancer, because these antigens might elicit specific T cell responses and lead to tumor regression (174, 175).

The selection of the autoantibody repertoire shared by patients with cancer and autoimmune disease can be further influenced by the immunological and pro-inflammatory properties of a given self antigen. It has been demonstrated that several self antigens, including asparaginyl and histidyl-tRNA sinthetases, U3/fibrillarin, ssDNA plus La/SS-B, and topoisomerase I can act as chemoattractants for leukocytes when released from damaged cells, thus inducing inflammation and autoimmunity (5, 176).

Finally, an autoimmune response may be due to molecular mimicry. In fact an immune response against an infectious agent can elicit a cross-reaction against human proteins with structural similarity (173).

5. BIOLOGICAL ACTIVITIES OF AUTOANTIBODIES TO SELF ANTIGENS

Autoantibodies occurring both in cancer patients and in autoimmune diseases exert several biological and pathogenic effects, that can modulate tumor growth and survival. Table 2 reports examples of biological effects exerted by autoantibodies to self antigens (9, 64, 94, 132, 133, 154, 177-202).

Kowal *et al.* reported that autoantibodies against dsDNA found in cerebrospinal fluid have the ability to cross-react with the NR2 glutamate receptor, leading to apoptotic neuronal death in the mouse hippocampus (177). In addition, these autoantibodies generate an inflammatory response due to their deposition as immune complexes in kidney and are able to penetrate into living cells and triggering apoptosis in mesangial and endothelial cells (9). dsDNA autoantibodies possess both *in vitro* and *in vivo* anti-tumor activities through the induction of apoptosis in myeloma and fibrosarcoma cell lines (9). Antinuclear antibodies (ANAs) increase the inflammation through the formation of immune complexes that can induce the production of cytokines or can deposit in the kidney tissue leading to systemic lupus erythematosus. The extracellular release of nuclear antigens is essential for the formation of these immune complexes. It has suggested that the pyroptosis can trigger antigens release in genetically predisposed individuals (178). Robitaille *et al*. demonstrated that autoantibodies to CENP-B inhibited the CENP-B-mediated production of IL-8 and also the transactivation of EGFR in vascular smooth muscle cells (179). A recent study demonstrated the enhanced phagocytosis by neutrophils in RA patients owing RF and anti-CCP autoantibodies. They showed that these autoantibodies indirectly increased the phagocytic capacity of neutrophils. In addition, RF and anti-CCP antibodies possess the ability to activate the complement system cascades, leading to the increase of the inflammatory process and then tissue damage in RA (180). Anti-citrullinated protein antibodies (ACPAs) in patients with RA are associated with inflammation and subsequent joint destruction and deformity. ACPAs bind to monocyte surface-expressed citrullinated GRP78 and stimulate TNF-α production and decrease let-7a miRNA expression. Lu *et al.* demonstrated that ACPAs contribute to inflammation by stimulating TNF-β production via binding to citrullinated GRP78 protein and following NF-κB activation on monocyte/macrophages (181). Furthermore, Lu *et al.* recently observed the ACPAs bind to citrullinated HSP-60 on the plasmamembrane of the osteosarcoma cell line Saos-2 and induce apoptosis through Toll-like receptor 4 (TLR4) signaling. Furthermore, ACPAs increase the expression of IL-6 and IL-8 in Saos-2 cells. RA patients with higher titer of anti-citrullinated HSP-60 antibodies showed severe joint damage, suggesting

Table 2. Examples of biological activities of autoantibodies to self antigens found in cancer and in autoimmune disease patients.

Autoantibodies	Biological activities	References
Anti-dsDNA	Apoptotic neuronal death (mouse hippocampus)	177
	Deposition of immune complexes in kidney and generation of inflammation, penetration in living cells, induction of apoptosis (mesangial and endothelial cells)	9
	Induction of apoptosis (myeloma and fibrosarcoma cells)	9
Anti-Nuclear antigens	Formation of immune complexes, increase of inflammation or deposition of immune complexes in the kidney	178
Anti-CENP-B	Inhibition of CENP-B-mediated production of IL-8 and transactivation of EGFR in vascular smooth muscle cells	179
Anti-CCP	Increase of phagocytic capacity of neutrophils and activation of complement system cascades	180
ACPA	Stimulation of TNF-α and -β production and decrease of let-7a miRNA expression; NF-κB activation on monocyte/macrophages via binding to citrullinated GRP78	181
	Induction of apoptosis through TLR4 signaling via binding to citrullinated HSP-60	182
ANCA	Activation of cytokine-primed neutrophils and production of ROS	183
Anti-TPO	Activation of ADCC and CDC; anti-proliferative activity in papillary thyroid cancer cells	64, 184
Anti-GRP78	Induction of proliferation and protection of prostate cancer cells from TNF-induced apoptosis	94
Anti-GRP78 (COOH-terminal domain)	Inhibition of cellular proliferation and induction of apoptosis in melanoma and prostate cancer cells	186, 187
	Decrease invasion and increase H_2O_2-induced apoptosis of ovarian cancer cells	188
Anti-HSP60, -HSP70	Enhancement of pro-inflammatory cytokines and chemochines production via TLR signaling in monocyte cells	189
Anti-Hu	Induction of neuronal cell death in the absence of T cell-mediated immune response or ADCC	190
Anti-Yo	Induction of cytotoxicity through a non apoptotic cell death in Purkinjie cells	191
Anti-α-enolase	Induction of apoptosis in endothelial and retinal cells	193, 194
	Reduction of the migration and invasion capacity of pancreatic ductal adenocarcinoma cells	195
Anti-Ribosomal P proteins	Inhibition of apolipoprotein B synthesis in hepatoma cells	196
	Impairment of memory and induction of apoptosis in brain cells and in Jurkat cells; inhibition of cell proliferation by inhibition of activation of Erk and Akt	196
	Delay of mammary carcinoma growth in a murine model of breast cancer	133
	Inhibition of *in vitro* cancer cell growth in colon cancer cells	134
Anti-ER	Erk activation and cell proliferation in breast cancer cells	142
Anti-AchR	Activation of apoptolysis in pemphigus vulgaris	197
Anti-VGCC	Block Ca2+ influx and inhibition of cell growth in SCLC cell lines	198
Anti-Phospholipids	Increase of leukocyte infiltration and tumor invasion in breast cancer	154
	Alteration of the inner mitochondrial membrane and of the normal apoptotic turnover of the syncytiotrophoblast	199
Anti-Dsg1, -Dsg3	Induction of apoptosis through the increase of Bax, p53, Fas ligand and receptor, and activation of caspases; activation of EGFR- and apoptosis (FasR)-mediated signaling pathways	200
Anti-Aquaporin-4	Induction of oligodendrocyte death, myelin loss and neuron death through complement-dependent astrocyte cytotoxicity	201
	Induction of astrocytopathy, in the absence of complement activation and immune cell infiltration in Devic's neuromyelitis optica	202

dsDNA: Double-strand DNA; CENP-B: Centromere nuclear protein-B; IL: Interleukin; EGFR: Epidermal growth factor receptor; CCP: Cyclic citrullinated peptide; ACPA: Anti-citrullinated proteins antibody; TNF: Tumor necrosis factor; NF-κb: Nuclear factor- κB; GRP78: Glucose-regulated protein 78; TLR: Toll-like receptor; HSP: Heat shock protein; ANCA: Anti-neutrophil cytoplasmic antibody; ROS: Reactive oxygen species; TPO: Thyroid peroxidase; ADCC: Antibody-dependent cellular cytotoxicity; CDC: Complement-dependent cytotoxicity; Erk: Extracellular signal-regulated kinases; Akt: Protein kinase B; ER: Estrogen receptor; AchR: Acetylcholine receptor; VGCC: Voltage-gated calcium channels; SCLC: Small cell lung cancer; Dsg: Desmoglein.

a role of membrane-expressed citrullinated HSP-60 and ACPAs in the pathogenesis of RA (182). Falk *et al*. demonstrated that anti-neutrophil cytoplasmic antibodies (ANCAs), through the binding to antigen on neutrophil surface, activate cytokine-primed neutrophils and produce reactive oxigen species (ROS). ANCAs also induces the release of primary granule contents. They suggested that ANCAs can release toxic oxygen radicals and noxious granule constituents leading to vascular injury in patients with pauci-immune necrotizing vasculitis and pauci-immune crescentic glomerulonephritis (183).

Anti-TPO autoantibodies play a role in the induction of thyroid dysfunction and also in the progression of the disease through cytotoxic mechanisms. TPO autoantibodies can damage thyroid cells by antibody- and complement-dependent cytotoxicity (ADCC and CDC). It has been demonstrated that monocytes are the effector cells and contribute with T cells to the destruction of thyroid gland mediated by anti-TPO antibodies in autoimmune thyroid disease (184). Anti-Tg autoantibodies are implicated in the destruction of thyroid gland and in the initiation of autoimmune thyroiditis (185). Furthermore, anti-TPO autoantibodies showed anti-proliferative activity in papillary thyroid cancer cells (64).

GRP78 is a chaperone protein of the endoplasmic reticulum and belong to the HSP70 family. It has been demonstrated that prostate cancer patients possess autoantibodies to GRP78, that bind to a site on the protein also recognized by its physiological agonist, α2-macroglobulin. These autoantibodies are able to induce proliferation of prostate cancer cells and protect them from TNF-induced apoptosis (94). In contrast, it has been reported that antibodies against the COOH-terminal domain of GRP78 inhibit cellular proliferation and induce apoptosis in melanoma and prostate cancer cells (186, 187). Patients with ovarian cancer possess autoantibodies against the COOH-terminal domain of GRP78 and these antibodies show the ability to decrease invasion and increase H_2O_2-induced apoptosis of ovarian cancer cells, suggesting a protective role of these antibodies in this type of cancer (188).

Several studies also demonstrated that autoantibodies against other HSPs exert biological activities. In particular anti-HSP60 autoantibodies are cytotoxic to endothelial cells, and anti-HSP60 and -HSP70 autoantibodies also enhance pro-inflammatory cytokines and chemochines production via TLR signaling in monocytic cells (189).

Anti-Hu and anti-Ri antibodies were shown to be internalized and accumulated into hippocampal and cerebellar neurons, but only anti-Hu antibodies were able to induce neurone cell death, in the absence of T cell-mediated immune response or antibody-dependent cellular cytotoxicity (190). It has also reported that anti-Yo antibodies have the capacity to induce citotoxicity through a non apoptotic cell death, but only in Purkinjie cells (191). Indeed, anti-Yo antibodies recognize cytoplasmic 62 kDa Yo antigen in Purkinje cell. This antigen plays an essential role in Purkinje cell survival and thus the binding of the antibody can induce cell death (192).

Anti-α-enolase autoantibodies were able to induce apoptosis in endothelial and in retinal cells (193, 194). In particular, these antibodies were able to inhibit the catalytic function of enolase, to deplete ATP, to elevate intracellular Ca2+, leading to Bax translocation to the mitochondria and release of cytochrome *c* into the cytoplasm (194). In addition, it has been reported that the *in vitro* and *in vivo* inhibition of α-enolase-1 with specific monoclonal antibodies reduces the migration and invasion capacity of pancreatic ductal adenocarcinoma cells. This activity could be a characteristic of patients with pancreatic cancer who possess autoantibodies against α-enolase (195).

Several studies analyzed the biological activities of anti-ribosomal P protein antibodies. Anti-ribosomal P protein antibodies inhibit apolipoprotein B synthesis by inducing cellular dysfunction in hepatoma cell lines. In Jurkat cells the antibodies are able to penetrate in cells and induce apoptosis (196). Other studies reported that anti-ribosomal P protein antibodies interact with several neuronal surface P antigen in hippocampal neurons, leading to impaired memory and brain cell apoptosis. Indeed, these antibodies penetrate in neuronal cells and inhibit cell proliferation through the inhibition of the activation of Erk and Akt proteins (196). We have demonstrated that the cellular stress induce an increased expression of the C-22 P0 epitope on cell membrane of pharynx cancer cell lines (132). In addition, it was reported that ectopic overexpression of P0 increases cell proliferation in breast and liver carcinoma cell lines. In our study, we demonstrated that BALB-*neu*T mice vaccinated with the human P0 protein showed a significant delay of mammary carcinoma growth and that the inhibition of tumor growth was associated with high serum levels of antibodies against P0 (133). In addition, we demonstrated the presence of a spontaneous humoral immune response to ribosomal P0 protein in colorectal cancer patients and the inhibition of *in vitro* cancer cell growth after C-22 P0 epitope targeting (134).

A recent study showed that antibodies against estrogen receptor (ER) found in patients with breast cancer, contribute to the pathogenesis of this cancer, because are able to act as estrogen agonists, leading to Erk activation and cell proliferation (143). Chernyavski *et al.* reported that patients with Phemphigus vulgaris (PV) produce antibodies that bind to AChR present on the cell membrane and on mitochondria.

The mitochondrial AChR can regulate the cytochrome *c* release by inhibiting mitochondrial permeability, leading to inhibition of the intrinsic pathway of apoptosis. In PV, this activity of mitochondrial AChR is abolished by the antibodies, leading to activation of apoptolysis (197). Autoantibodies to presynaptic P/Q-type VGCC in Lambert-Eaton myasthenic syndrome are able to block Ca2+ influx through voltage-gated calcium channels in SCLC cell lines, thus suggesting that *in vivo* they may interfere with tumor growth (198).

Several studies showed that anti-phospholipids autoantibodies exert different biological activities. Wu *et al.* reported that the presence of

anti-phospholipids autoantibodies is associated with invasive tumors in breast cancer patients. These autoantibodies are capable of increasing leukocyte infiltration and tumor invasion, leading to acceleration of tumor angiogenesis and progression. Anti-phospholipids autoantibodies can induce the expression of Tissue Factor (TF) and VEGF in endothelial cells and monocytes (154). In addition, it has been reported that anti-phospholipids autoantibodies are internalized into the syncytiotrophoblast and affect the inner mitochondrial membrane and alter the normal apoptotic turnover of the syncytiotrophoblast. Indeed, anti-phospholipids autoantibodies are able to increase proton leak through the inner mitochondrial membrane and to decrease the ability of the ATPase to produce ATP, leading to necrosis (199). Anti-Dsg1 and anti-Dsg3 are the main autoantibodies found in patients with PV. These autoantibodies are able to induce apoptosis through the increase of Bax, p53, Fas ligand and receptor (FasR) and activation of caspases. In addition, PV autoantibodies are able to bind to EGFR and to activate EGFR- and apoptosis (FasR)-mediated signaling pathways (200). Several studies have been demonstrated that antibodies to aquaporin-4 have the ability to diffuse in all central nervous system structures, including the optic nerve and spinal cord, and to induce oligodendrocyte death, myelin loss and neuron death. These effects are mediated by complement-dependent astrocyte cytotoxicity, through leukocyte infiltration, cytokines release and blood-brain barrier disruption (201). A recent report also demonstrated that aquaporin-4 antibodies can induce astrocytopathy, in the absence of complement activation and immune cell infiltration in Devic's neuromyelitis optica (202).

6. ASSOCIATION OF AUTOANTIBODIES TO SELF ANTIGENS WITH PARANEOPLASTIC AUTOIMMUNE SYNDROMES

The presence of autoantibodies to self antigens can be associated with paraneoplastic autoimmune syndromes and revealed by the occurrence of neurological syndromes as well as metabolic, rheumatic, cutaneous and haematological disorders in cancer patients due to the biological activities of the elicited immunoglubulins (40, 98, 203-228). Autoantibodies to onconeural antigens can induce in cancer patients cerebellar degeneration (anti-Hu, anti-neuronal Na(+)/K(+) ATPase, anti-ZIC4, anti-Yo, anti-CV2, anti-Tr, anti-mGluR1, Anti-Ma2, anti-Ri and anti-VGCC autoantibodies), encephalomyeloneuropathy (anti-PCA2, anti-Hu, anti-CV2, anti-Amphiphysin and anti-VGCC autoantibodies), sensory neuropathy (anti-Hu, anti-CV2 and anti-amphiphysin autoantibodies), retinopathy (anti-CV2, anti-TRMP1 and anti-Recoverin autoantibodies), DADS neuropathy (anti-MAG and anti-CENP-F autoantibodies), myasthenia gravis (anti-AchR autoantibodies), Lambert-Eaton myasthenic syndrome (anti-SOX1 and anti-VGCC autoantibodies), neuromyelitis optica (anti-Aquaporin-4 autoantibodies), Stiff-person syndrome (anti-Amphiphysin autoantibodies) and limbic encephalitis (anti-Hu, anti-Ma2, anti-NMDAR and anti-AMPAR autoantibodies) (98, 203-219). Anti-GAD autoantibodies induce paraneoplastic diabetes mellitus in SCLC or PGA2 in hepatocellular carcinoma patients (220, 221). Paraneoplastic pemphigus is characterized by the occurrence of autoantibodies to plakin family proteins in patients with haematological neoplasms, carcinomas and melanoma (222). The occurrence of anti-nuclear antibodies induces the lupus-like syndrome, the polyarteritis nodosa and the Raynaud's phenomenon in cancer patients (223). Anti-CCP autoantibodies were reported to induce polyarthritis in lung cancer patients (224). The paraneoplastic autoimmune multiorgan syndrome can arise in cancer patients for the presence of anti-plakins, anti-plectin and a2-macroglobulin-like-1 molecule autoantibodies (225, 226). Finally, anti-red cells and -platelets autoantibodies can induce autoimmune hemolytic anemia and thrombocytopenia in cancer patients, respectively (40, 227, 228). An example of the occurrence of autoantibodies in cancer patients associated with paraneoplastic autoimmune syndromes are reported in Table 3.

7. ROLE OF AUTOANTIBODIES TO SELF ANTIGENS AS BIOMARKERS FOR CANCER DETECTION AND CANCER PATIENTS PROGNOSIS

The presence of autoantibodies to self-antigens has been investigated as a marker for cancer detection and for predicting survival of cancer patients. Examples of these autoantibodies are reported in Table 4. Several techniques were used to discover novel tumor antigens able to elict autoantibodies, including serological analysis of tumor antigens by recombinant cDNA expression cloning (SEREX), serological proteome analysis (SERPA), multiple affinity protein profiling (MAPPing) and high-density protein microarrays (229). However, the confirmation of the association of antibodies to tumor antigens with clinical parameters, and thus their potential use as biomarkers for early detection of cancer and cancer patients prognosis, needs validation by employing recombinant protein ELISA (Enzyme-Linked Immunosorbent Assay), protein microarrays and bead-based immunoassay (166, 229). However, the usefulness of autoantibodies as markers for cancer patients prognosis is still controversial (229). In addition, immune response to tumor antigens could also be enhanced or decreased after standard therapies. For example, we have demonstrated that radiotherapy increased the levels of autoantibodies to P0 protein and decreased those to collagens, fibronectin and HSP90 in prostate cancer patients (74). In addition, a recent study reported that the levels

Table 3. Pattern of autoantibodies to self antigens detected in cancer patients and associated with paraneoplastic syndromes.

Autoantibodies	Cancer site or histological subtype	Paraneoplastic Autoimmune Syndromes	References
		Neurological Syndromes	
Anti-PCA2	SCLC	Encephalomyeloneuropathy	208
Anti-Hu (ANNA-1)	SCLC, prostate, neuroblastoma, Hodgkin lymphoma	Encephalomyelitis, sensory neuropathy, cerebellar ataxia, limbic encephalitis	98, 203
Anti-neuronal Na^+/K^+ ATPase	Colon	Brainstem and cerebellar syndrome	204
Anti-ZIC4	Ovary, SCLC	Paraneoplastic cerebellar syndrome	205, 206
Anti-Yo (PCA-1)	Ovary, breast, uterus	Paraneoplastic cerebellar degeneration	98, 207
Anti-CV2/CRMP-5	SCLC, thymoma	Encephalomyeloneuropathy with corea, encephalomyelitis, sensory-motor neuropathy, uveitis, retinopathy, cerebellar ataxia	98, 208
Anti-Aquaporin-4	Lung, ovarian teratoma	Neuromyelitis optica, longitudinally extensive transverse myelitis	216, 217
Anti-Amphiphysin	SCLC, breast	Stiff-person syndrome, sensory-motor neuropathy, encephalomyelitis	98
Anti-SOX1	SCLC	Lambert-Eaton myasthenic syndrome	215
Anti-MAG	Colon-rectum	DADS neuropathy	214
Anti-CENP-F	Colon-rectum	DADS neuropathy	214
Anti-Ri (ANNA-2)	SCLC, breast	Opsoclonus-myoclonus, cerebellar ataxia	98
Anti-Ma2 (Ta)	Testis, lung	Limbic-diencephalic encephalitis, subacute cerebellar degeneration, myeloradiculopathy	98, 210
Anti-TRMP1	Melanoma	Retinopathy	212, 213
Anti-Recoverin	SCLC	Retinopathy	98
Anti-Tr (PCA-Tr)	Hodgkin' disease	Cerebellar ataxia	98
Anti-mGluR1	Prostate	Cerebellar degeneration	209
Anti-AchR	Thymoma	Miasthenia gravis	98
Anti-NMDAR	Ovarian teratoma	Limbic Encephalitis	218
Anti-VGCC	SCLC, breast, lymphoma	Encephalopathy, ataxia, myelopathy, neuropathy, neuromuscular junction disorder, myopathy, Lambert-Eaton myasthenic syndrome, subacute cerebellar degeneration	98, 211
Anti-AMPAR	Breast	Limbic encephalitis	219
		Metabolic Sindromes	
Anti-GAD	SCLC, HCC	Diabetes mellitus, PGA2	220, 221
		Skin and Mucous Membrane Syndromes	
Anti-Plakin family proteins (desmoplakins I and II, BP230, periplakin, Envoplakin, Dsg-3 and/or Dsg-1)	Haematological neoplasms, carcinomas and melanoma	Pemphigus	222
Anti-Plakins, Anti-Plectin, α2-macroglobulin-like-1 molecule	NHL, CLL, Castleman disease, pancreas, colon, breast, prostate, liver, tongue, bronchi, cervix, kidney	Paraneoplastic autoimmune multiorgan syndrome	225, 226
		Rheumatic Syndromes	
Anti-CCP	Lung	Polyarthritis	224
ACA, ANA	Liver, ovary, testis, kidney, melanoma, lymphoma, multiple myeloma	Raynaud's phenomenon	223
ANA	Ovary, breast, head and neck, meningioma	Lupus-like syndrome	223
ANCA	Kidney, colon	ANCA-associated vasculitis	223

ANA	Stomach, lung angiomatoid fibrous histiocytoma	Polyarteritis nodosa	223
		Hematological Syndromes	
Anti-red cells	B cell lymphoma, colon, leukemia, kidney	AIHA	227, 228
Anti-phospholipids, platelet glycoproteins	Lymphoproliferative disease	AITP	228

PCA: Purkinje cell cytoplasmic antibody; SCLC: Small cell lung cancer; ANNA: Anti-neuronal nuclear antibody; ZIC4: Zinc finger protein of cerebellum; CV2/CRMP-5: Collapsin response-mediator protein-5; MAG: Myelin-associated glycoprotein; DADS: Distal acquired demyelinating symmetric; CENP-F: Centromere nuclear protein-F; TRMP1: transient receptor potential cation channel, subfamily M, member 1; mGluR1: Metabotropic glutamate receptor type 1; AchR: Acetylcholine receptor; NMDAR: N-methyl-D-aspartate receptor; VGCC: Voltage-gated calcium channels; AMPAR: Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; GAD: Glutamic acid decarboxylase; HCC: Hepatocellular carcinoma; PGA2: Polyglandular autoimmune syndrome type 2; Dsg: Desmoglein; NHL: Non Hodgkin lymphoma; CCP: Cyclic citrullinated peptide; ACA: Anti-centromere antibody; ANA: Anti-nuclear antibodies; ANCA: Anti-neutrophil cytoplasmic antibodies; AIHA: Autoimmune hemolytic anemia, AITP: Autoimmune thrombocytopenia.

Table 4. Examples of autoantibodies to self antigens proposed as biomarkers or associated with cancer patients prognosis.

Type of tumor	Autoantibodies	Signature of cancer as compared to control groups or prevalence	Survival or Prognosis or Recurrences	References
Breast cancer	Anti-P0	Significant (Prevalence of 10.6%)	No correlation with clinical stage	133
	Anti-Annexin XI-A, -Ku, -Ribosomal protein S6	Significant	NA	231
	Anti-MUC-1 glycoforms	Significant	Lower incidence of metastases	232
	Anti-CENP-B	Signifcant (Prevalence of 33%)	Longer DFS and OS	233
	Anti-p53	Significant	Shorter 5-year survival	234
	Anti-p53	Prevalence of 9%	Shorter survival	235
	Anti-SOX2	Significant (Prevalence of 18.4%)	NA	236
	Anti-FKBP52, -PPIA, -PRDX2	Significant	NA	237
	Anti-PARP1, -BRCA2	Significant (Prevalence of 15.3% and 36.6% respectively)	NA	238
	Anti-HER2, -p53, -CEA, -Cyclin-B1	Significant	NA	239
	Anti-EPHA2, -IGFBP2, -CST2, -GAL1, -HER-2, -LAMC2, -ANGPTL4, -DKK1, -MUC1, -SSR2, -SPINT2, -SPON2	Significant	NA	240
	Anti-c-Myc, -Survivin, -Cyclin-B1, -Cyclin-D1, -p62, -p53, -p16, -CDK2	Significant (Sensitivity of 61%, specificity of 89%)	NA	241
	Anti-Imp1, -p16, -Koc, -Survivin, -Cyclin-B1, -c-Myc	Significant (Sensitivity of 67.3%, specificity of 92.2%)	NA	242
	Anti-p90/CIP2A	Significant	NA	242
	Anti-IMP2/p62	Significant (Prevalence of 14.3%)	NA	242
	Anti-MDM2, -c-Myc	Significant	Shorter DFS (anti-c-Myc)	33
	Anti-HuC or -HuD	Significant (Prevalence of 23.3%)	NA	96
	Anti-p53	Significant (Prevalence of 20.6%)	Poor prognosis	244
	Anti-p53	Significant	No association with survival or disease stage	245, 246, 247
	Anti-ANXA1	Significant (Sensitivity of 23%, specificity of 90%)	NA	248
	Anti-CCNY	Significant (Sensitivity of 23.5%, specificity of 95.5%)	Poor prognosis	249
	Anti-IGFBP-2	Significant (Sensitivity of 73.2%, specificity of 90%)	NA	250
	Anti-p16	Significant (Sensitivity of 19.7%, specificity of 60.6%)	Association with advanced stage	251
	Anti-Chromogranin A	Significant (Sensitivity of 47.6%, specificity of 80.0%)	NA	252

Lung cancer	Anti-SMOX, -NOLC1, -MALAT1, -HMMR	Significant (Sensitivity of 47.5%, specificity of 97.3%)	NA	253
	Anti-NY-ESO-1, -XAGE-1, -ADAM29, -MAGEC1	Significant (Sensitivity of 33%, specificity values of 96%)	Association with advanced stage	254
	Anti-p53, -NY-ESO-1, -CAGE, -SOX2, -GBU4-5,-Annexin 1	Significant (Sensitivity of 34%, specificity of 91%)	No differences between disease stage	255
	Anti-14-3-3ζ, -c-Myc, -MDM2, , -p16, -p53, -Nucleophosmin, -Cyclin-B1	Significant (Sensitivity of 68.9%, specificity of 79.5%)	NA	256
	Anti-KIAA037, -ROCK1, -PRKCB1, -TACC2, -C14ORF145, -ARFGAP3, -YBX1, - SOX2 homologous	Significant (Prevalence of 15%)	NA	257
	Anti-monophosphate dehydrogenase, -fumarate hydratase, -α-enolase, endoplasmic reticulum protein 29, -Annexin 1, -hydrosteroid 17-β dehydrogenase, -MTAP	Significant	NA	258
	Anti-TTC14, -BRAF, -CTAG1B, -ACTL6B, -MORC2	Significant	NA	259
	Anti-p62, -BIRC, -Livin-1, -p53, -PRDX, -NY-ESO-1, -Ubiquitin	Significant	NA	260
	Anti-p53	NA	Lower probability of OS and DFS	262
	Anti-p53	NA	No association with survival	265
Esophagus cancer	Anti-CD25	Significant	NA	266
	Anti-FOXP3	Significant (Sensitivity of 22.7%, specificity of 95%)	NA	267
	Anti-p16	Significant (Prevalence of 5.7%)	NA	268
	Anti-c-Myc, -HCCR, -p53, -p62	Significant	NA	269
Gastric cancer	Anti-p53	Significant	Longer survival	270
	Anti-p53	Prevalence of 20.3%	Poor prognosis	271
	Anti-p53	Prevalence of 31%	NA	272
	Anti-p53	Prevalence of 12.2%	Shorter survival	273
	Anti-GRP78	Prevalence of 28.3%	NA	274
	Anti-MAGEA4, -CTAG1, -p53, -ErbB2_C, -SDCCAG8	Significant	NA	275
	Anti-p53, -Koc, -p62, -c-Myc, -IMP1, -Survivin, -p16	Prevalence of 64%	NA	276
	Anti-CT antigens (-MAGEC1, -MAGEA3, -CTAG2, -CTAG1B)	Significant	NA	277
Colorectal cancer	Anti-dsDNA	Significant	Less incidence of recurrences	10
	Anti-p53	Significant	No association with survival	31
	Anti-P proteins	Significant (Prevalence of 10.4%)	NA	134
	Anti-p53	Prevalence of 25%	Shorter survival	278
	Anti-PIM1, -MAPKAPK3, -ACVR2B	Significant (Sensitivity of 84.1%, specificity of 71.4%)	NA	279
Hepatocellular carcinoma	Anti-Nucleophosmin 1	Significant (Prevalence 24.4%)	NA	26
	Anti-c-Myc, -p53, -Cyclin-B1, -p62, -Koc, -IMP, -Survivin	Significant (Prevalence of 59.9%)	NA	42
	Anti-p53	Significant	Shorter survival	280
	Anti-p53	Significant	NA	281
	Anti-Sui1, -RalA	Significant (Prevalence of 11.7% and 19.5%, respectively)	NA	282
	Anti-DDX3, -eEF2, -AIF, -hnRNP A2, -PBP, -TIM	Significant	NA	283

	Anti-AFP, -Gankyrin, -GPC-3, -IMP1, -p62, -Koc, -p53, -c-Myc, -Cyclin-B1, -HuD, -Survivin, -MAGEA4, -p16, -SOX-2, -CAGE, -NY-ESO-1, -GBU4-5	21 TAAs (Specificity 92%, sensitivity 45%; high risk positivity 21%)	NA	284
	Anti-p53	NA	Shorter survival	285
	Anti-p53	Prevalence of 7%	Higher survival rate without recurrence	286
	Anti-AFP	Significant	NA	287, 288
Pancreatic cancer	Anti-DDX48	Significant (Prevalence of 33.33%)	NA	289
Ovarian cancer	Anti-IMP, -IMP2/p62	Significant (Prevalence of 26.5% and 29.4% respectively)	NA	43
	Anti-PARP1, - BRCA1	Significant (Prevalence of 29.4% and 50.0% respectively)	NA	238
	Anti-p53	Prevalence of 15%	No association with OS	290
	Anti-p53	Prevalence of 25% (serum) and of 19% (ascites)	Unfavorable DFS and OS (Ascites autoantibodies)	291
	Anti-p53	Significant	Improved OS	292
	Anti-p53	Prevalence of 12.4%	No association with survival	293
	Anti-p53	Prevalence of 19%	Shorter OS and DFS	294
	Anti-CFL1, -EZR, -JUP, -HIST1H1C, -HNRNPAB, -HSPA9, -PDZD11, -PFN1, -PP1A, -SERF2, -TUBA1C	Significant	NA	295
	Anti-p53, -PTGFR,-PTPRA, -ACSBG1, -AFP, -CSNK1A1L, -DHFR, -PRL, -PSMC1, -RAB7L1, -SCYL3	Significant	NA	296
	Anti-p53	NA	No association with OS (pooled uni-multivariate HRs). Association with a better OS with a pooled multivariate HRs (4 studies)	297
Prostate cancer	Anti-protein biosynthesis, -translation, -cytoskeleton, -nucleus and organelles	Significant	NA	298
	Anti -60S ribosomal protein L7, -MARCKS1 homologous	Significant (discrimination between prostate cancer patients and patients with prostatic benign hyperplasia)	NA	299
	Anti-MUT, -RAB11B, -CSRP2, -SPOP, -ZNF671	Discrimination between prostate cancer patients with low from those with high inflammation (Sensitivity of 80% and specificity of 67%)	NA	300
Pediatric ALK-positive anaplastic large cell lymphoma	Anti-ALK	Prevalence of 38%	Lower incidence of relapse	301

NA: Not Available; MUC: mucin; CENP-B: centromere nuclear protein-B; DFS: disease-free survival; OS: overall survival; FKBP: FK506 binding protein; PPIA: Peptidylprolyl isomerase A; PRDX: peroxiredoxin; PARP1: Poly(ADP-ribose) polymerase 1; BRCA2: Breast related cancer antigen 2; HER2: Receptor tyrosine-protein kinase erbB-2; CEA: carcinoembryonic antigen; EPHA2: Ephrin type-A receptor 2; IGFBP2: Insulin-like growth factor-binding protein 2; CST2: Cystatin-SA; GAL1: Galactokinase 1; LAMC2: Laminin subunit gamma 2; ANGPTL4: Angiopoietin-like 4; DKK1: Dickkopf-related protein 1; SSR2: serine-rich repeat protein 2; SPINT2: Kunitz type serine peptidase inhibitor 2; SPON2: spondin 2; p90/CIP2A: cancerous inhibitor of PP2A; IMP2/p62: IGF2 mRNA-binding protein 2; CCNY: Cyclin Y; SMOX: spermine oxidase; NOLC1: Nucleolar and coiled-body phosphoprotein 1; MALAT1: Metastasis-associated lung adenocarcinoma transcript 1; HMMR: Hyaluronan mediated motility receptor; XAGE-1: X antigen family member-1; ADAM29: ADAM metallopeptidase domain 29; MAGEC1: MAGE family member C1; CAGE: Cancer-associated gene; ROCK1: Rho-associated, coiled-coil-containing protein kinase 1; PRKCB1: Protein kinase C beta 1; TACC2: Transforming acidic coiled-coil-containing protein 2; C14ORF145: Human centrosomal protein of 128 kDa; ARFGAP3: ADP-ribosylation factor GTPase activating protein 3; YBX1: Y box binding protein 1; MTAP: Methylthioadenosine phosphorylase; TTC14: tetratricopeptide repeat domain 14; BRAF: B-Raf proto-oncogene, serine/threonine kinase; ACTL6B: Actin like 6B; MORC2: MORC family CW-type zinc finger 2; CTAG1: cancer/testis antigen 1; BIRC: Baculoviral inhibitors of apoptosis repeat containing; CD25: Alpha chain of the IL-2 receptor; FOXP3: Forkhead box P3; GRP78: Glucose-regulated protein 78; SDCCAG8: Serologically defined colon cancer antigen 8; dsDNA: Double-strand DNA; MAPKAPK3: MAP kinase-activated protein kinase 3; ACVR2B: Activin receptor type-2B; RalA: Ras-related protein Ral-A; DDX: DEAD-box protein; eEF2: Eukaryotic elongation factor 2; AIF: Apoptosis-inducing factor; hnRNP: Heterogeneous nuclear ribonucleoprotein; PBP: Prostatic binding protein; TIM: T-cell immunoglobulin and mucin-domain; AFP: Alpha-fetoprotein; GPC-3: Glypican-3; CFL1: Cofilin 1; EZR: Ezrin; HIST1H1C: Histone cluster 1 H1 family member C; HSPA9: Heat shock protein family A (Hsp70) member 9; PDZD11: PDZ domain-containing protein 11; PFN1: Profilin-1; PP1A: Protein phosphatase 1A; SERF2: Small EDRK-rich factor 2; TUBA1C: Tubulin alpha 1C; JUP: Junction plakoglobin; PTGFR: Prostaglandin F receptor; PTPRA: Protein tyrosine phosphatase, receptor type A; ACSBG1: Acyl-CoA synthetase bubblegum family member 1; CSNK1A1L: Casein kinase 1 alpha 1 like; DHFR: Dihydrofolate reductase; PRL: Prolactin; PSMC1: Proteasome 26S subunit, ATPase 1; HR: Hazard ratio; MUT: Methylmalonyl-CoA mutase; CSRP2: Cysteine and glycine-rich protein 2; SPOP: Speckle-type POZ protein; ZNF671: Zinc finger protein 671; ALK: Anaplastic lymphoma kinase.

of autoantibodies against galectin-3 could be useful to predict the efficacy of chemotherapy in patients with lung adenocarcinoma (230).

Autoantibodies to a single antigen including p53, CENP-B, annexin XI-A, the p80 subunit of the Ku antigen, ribosomal protein S6, ribosomal P0 protein, p90/CIP2A, SOX2, IMP2/p62 and glycoforms of MUC1 could significantly discriminate breast cancer patients from healthy donors (26, 133, 231-236). To improve cancer detection, recent studies have analyzed the presence of autoantibodies to a panel of antigens. For example autoantibodies to FKBP52, PPIA, and PRDX2, to PARP1 and BRCA1/BRCA2 or to HER2, p53, CEA, and cyclin-B1 were significantly detected in cancer patients as compared to healthy controls (237-239). Overall a combination of autoantibodies against different antigens allowed to discriminate cancer patients from healthy donors and autoantibodies to HER2 and p53 could be detected in prediagnostic cancer patient sera (239-242). Anti-p53 autoantibodies were associated with a shorter patients survival (234, 235). Conversely, the presence of anti-CENP-B autoantibodies was associated with prolonged DFS and OS, and that to MUC1 glycoforms to a lower incidence of metastases and increased time to metastasis (232, 233).

Several studies have demonstrated the presence of significant levels of autoantibodies in lung cancer patients as compared to healthy donors (33, 96, 243-265). Circulating autoantibodies to individual p53, annexin A1-derived peptide antigens, CCNY, IGFBP-2, p16, chromogranin A-derived peptides were significantly higher in cancer patients than control subjects (243-252). Autontibodies to two or more antigens including HuC/HuD, SMOX/NOLC1/MALAT1 and HMMR, NY-ESO-1/XAGE-1/ADAM29, and MAGEC1, p53/NY-ESO-1/CAGE, GBU4-5/Annexin 1 and SOX2, 14-3-3ζ/-c-Myc/MDM2/Nucleophosmin 1/p16/p53 and cyclin-B1, p62/BIRC/Livin-1/p53/Peroxiredoxin/NY-ESO-1 and Ubiquitin, and several other antigens combination were analyzed for improving the sensitivity and specificity of the assays for discriminating cancer patients from healthy donors (33, 96, 253-260). In addition, autoantibodies to p16, NY-ESO-1, XAGE-1, ADAM29, and MAGEC1 were associated with advanced disease stages, those to c-Myc were related to shortened DFS and those to p53 or to CCNY were linked to shorter survival or worse prognosis (33, 243, 244, 249, 251, 254, 261, 262). Conversely, ANAs were linked to a better patients survival (263). Other reports detecting autoantibodies to p53 could not reveal any association with patients survival or disease stage (245-247, 255, 264, 265).

Serum of patients with digestive tract tumors was analyzed for the presence of autoantibodies to self antigens too (266-277). The prevalence of autoantibodies to CD25, or FOXP3, or p16 was significantly higher in esophageal squamous cell carcinoma patients than in the control groups (266-268). In addition, autoantibodies to a panel of four antigens (c-Myc, HCCR, p53 and p62) showed high diagnostic accuracy for esophageal cancer (269). Autoantibodies to p53 or GRP78 were detected with higher prevalence in gastric carcinoma patients than in healthy donors (270-274). The survival time of gastric carcinoma patients testing positive for anti-p53 autoantibodies was significantly longer than that of testing negative patients (270). However, p53 autoantibodies were predictor of an unfavorable prognosis in other studies (271, 273). Combination of autoantibodies against five tumor-associated antigens (TAAs) (MAGEA4 + CTAG1 + TP53 + ERBB2_C + SDCCAG8) was able to increase the percentage of positive gastric cancer patients (275). In the study performed by Zhou *et al.*, the sensitivity and the specificity for autoantibodies against seven TAAs (Anti-p53, -Koc, -p62, -c-Myc, -IMP1, -Survivin and -p16) in diagnosing gastric cardia adenocarcinoma reached up to 64% and 87%, respectively (276). By applying a T7 phage display-based serological analysis of recombinant cDNA expression libraries technique it was identified a representative set of antigens eliciting humoral responses in gastric cancer patients. 45-autoantibodies signature could discriminate gastric cancer patients from healthy donors (277).

The prevalence of autoantibodies to dsDNA or p53 or P proteins were higher in patients with colorectal cancer than in healthy subjects (10, 31, 134, 278). The prevalence of simultaneous autoantibodies to PIM1, MAPKAPK3, and ACVR2B were able to discriminate between colorectal cancer and control samples with a sensitivity of 84.1% and a specificity of 71.4% (279). No correlation was found between colorectal cancer patients survival and anti-p53 autoantibodies (31). Conversely, in another study a shorter survival characterized patients positive for anti-p53 autoantibodies (278). In addition, patients with anti-dsDNA autoantibodies showed a less incidence of recurrences after a 3-year follow-up (10).

The prevalence of autoantibodies against p53, or, nucleophosmin was higher in HCC patients than that in healthy donors (26, 280, 281). Autoantibodies to multiple tumor-associated antigens were shown to enhance detection of HCC showing higher prevalence in HCC patients than in chronic hepatitis and normal donor sera (42, 282-284). A shorter patients survival time was observed in HCC patients displying anti-p53 autoantibodies (280, 285). On the other hand, a study reported that HCC patients having anti-p53 autoantibodies had higher survival rate without recurrence (286). In addition, autoantibodies to α-fetoprotein were more prevalent in HCC patients

than in healthy donors or liver cirrhosis and chronic hepatitis patients (287, 288).

Reactivity to DDX48 was observed in 20 of 60 (33.33%) pancreatic cancer patients while none of the 60 normal individuals analyzed had anti-DDX48 autoantibodies (289).

The high prevalence of autoantibodies to p53, IMP1 and IMP2/p62, PARP1 and BRCA1, or to a panel of different antigens suggested that autoantibodies could be potential biomarkers in immunodiagnosis of ovarian cancer (43, 238, 290-296). However, there is not an agreement for the prognostic value of anti-p53 autoantibodies. Shortened OS and RFS or unfavorable DSF and OS were reported in ovarian cancer patients harboring serum or ascites anti-p53 autoantibodies, respectively (291, 294). Conversely, one study reported that anti-p53-autoantibodies were prognostic for improved OS (292). Other studies reported no association with patients survival (290, 293). Finally, the presence of anti-p53 autoantibodies was significantly associated to a better OS when only multivariate HRs were pooled together (4 studies) (297).

Autoantibodies to multiple antigens were detected in prostate cancer patients (298-300). Massoner *et al.* found autoantibodies to 408 different antigens and reported that 174 of these were solely detected in cancer patients compared to healthy donors (298). Autoantibodies to antigens fragments with homology to 60S ribosomal protein L7, and MARCKS1 were able to discriminate prostate cancer patients from patients with benign prostatic hyperplasia (299). The presence of autoantibodies to MUT, RAB11B, CSRP2, SPOP and ZNF671 was able to distinguish prostate cancer patients with low from those with high inflammation with a sensitivity of 80% and a diagnostic specificity of 67% (300). None of these studies investigated the prognostic values of autoantibodies.

Finally, high antibody titers to ALK (prevalence 38%) correlated with significantly lower cumulative incidence of relapses in pediatric anaplastic lymphoma kinase-positive anaplastic large cell lymphoma (301).

8. PARANEOPLASTIC NEUROLOGICAL SYNDROMES, EFFECTS OF THERAPY TARGETING IMMUNE-CHECKPOINT RECEPTORS AND Tregs DYSREGULATION IN AUTOIMMUNE DISEASE PATIENTS: THE CROSSROAD BETWEEN AUTOIMMUNITY AND IMMUNE RESPONSE IN CANCER PATIENTS

From studies regarding patients with paraneoplastic neurological syndromes we have learned that antibodies to self antigens might reflect the attempt to counteract tumor growth and might affect cancer patients survival (302, 303). Patients survival analysis showed a significantly shorter median survival time from the diagnosis of SCLC in SCLC patients without Lambert-Eaton myasthenic syndrome than in those with Lambert-Eaton myasthenic syndrome (304). Dalmau *et al*. analyzed 71 patients with “paraneoplastic” encephalomyelitis or sensory neuronopathy, or both who had serum anti-Hu antibodies. Most of the patients (78%) had small-cell lung cancer. In 9 patients no tumor was revealed. Thus, the authors searched for the presence of the tumor that when detected was frequently small and localized or was detected only at autopsy (305). Peterson *et al*. reviewed the clinical findings in 55 patients with cerebellar degeneration associated with the anti-Yo autoantibodies. Fifty-two of them had cancers, mainly limited to the involved organs (breast and gynecological tract) and local lymph nodes. One woman had lung adenocarcinoma, and in three no malignancy was identified. In 34 of 52 patients with cancer, the neurologic syndrome preceded the cancer diagnosis and in many led to the diagnosis (306). Graus *et al*. found that the presence of anti-Hu autoantibodies in patients with paraneoplastic encephalomyelitis/sensory neuropathy and SCLC is a strong and independent predictor of complete response to the therapy and that this feature accounts for the association between anti-Hu autoantibodies and longer cancer patients survival (307). Honnorat *et al*. found that the median survival time was significantly longer in patients with SCLC and anti-CV2/CRMP5 autoantibodies as compared to patients with SCLC and anti-Hu autoantibodies, thus suggesting that the prognosis of the same type of tumor may be dependent on the type of onconeural autoantibodies (308). Hetzel *et al.* suggested that the immune response evoked against cancer cells and probably cross-reactive with cerebellar cells, might affect the metastatic process. Indeed, the authors found that in 8 patients who had primary stage III gynecological cancer and anti-Purkinje cell autoantibodies as compared to 24 control patients without paraneoplastic cerebellar degeneration there was no difference in the volume of the primary tumor but a significantly smaller volume of the metastatic tumor in the autoantibodies-positive group (309). In a prospective analysis of the presence of self-antigens autoantibodies and of mortality in 238 SCLC patients, Gozzard *et al*., observed an independent survival advantage associated with anti-neuronal nuclear antibodies (ANNAs) (310). On the other hand, Rojas *et al*. by retrospectively analyzing the clinical outcome and prognostic factors in a series of 34 patients with paraneoplastic cerebellar degeneration and anti-Yo autoantibodies found that the overall prognosis of cancer patients was rather poor, particularly for patients with gynecologic tumors (311). In addition, in some reports tumor was shown to regress in patients

with paraneoplastic neurological degeneration (303). Zaheer *et al*. described a case of small SCLC that spontaneously regressed in concomitant with the occurrence of a paraneoplastic neurological syndrome and the presence of anti-neuronal antibodies (312). Darnell described a spontaneous regression of a lung mass in a patient with both the anti-Hu and atypical anti-neuronal antibodies and subacute sensory neuropathy (302). In addition they found that one patient survived 8 years free of disease and was positive for the anti-Hu autoantibodies and another patient survived 6 years after spontaneous tumor regression and had anti-neuronal autoantibodies (302). Mawhinney *et al.* reported that a paraneoplastic sensory neuropathy with high titers of anti-Hu autoantibodies, was associated with lung tumor regression (313). Similarly, Gill *et al*. reported a case of a patient with anti-Hu autoantibodies associated paraneoplastic sensory neuronopathy who had a spontaneous regression of the small cell lung cancer (314). Hirano *et al.* observed a partial spontaneous regression of a SCLC tumor associated with a progression of paraneoplastic sensory neuropathy and the presence of anti-neuronal autoantibodies in a 55-year-old woman (315). Villers *et al.* reported a paraneoplastic amyopathic dermatomyositis associated with the regression of a primary melanoma (316).

The microenvironment within the tumor can support the growth of cancer cells trough the release of growth factors and immunosuppressive cytokines by endothelial cells, immune cells and mesenchymal stromal cells (MSC) (317). Among the others, Tregs are key regulators of the immune responses, avoiding abnormal immune system activation and autoimmunity (318). Tregs have shown to suppress the activity of effector T cells, Natural Killer (NK) cells and dendritic cells either by cell-cell contact or by the secretion of immunosuppressive cytokines (IL-10 and TGFβ) and indoleamine-2,3-dioxygenase (IDO) (318). On the other hand, MDSCs stimulate chronic tissue inflammation and suppression of immune response by the release of reactive oxygen species, nitric oxide, arginase-1 and cytokines and by the recruitment and induction of Tregs and immunosuppressive tumor-associated macrophages (TAM) in the tumor microenvironment (318). Several inhibitory pathways are involved in maintaining immune self-tolerance thus preventing autoimmune diseases and exaggerate immune responses to pathogens (319). The occurrence of an autoimmune disease is a sign of a merged deficiency of both central and peripheral immune tolerance inducing the activation of autoreactive T cells (5). Tregs express immune-checkpoint receptors, including cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), programmed cell death protein 1 (PD1), T cell membrane protein 3 (TIM3), adenosine A2a receptor (A2aR), lymphocyte activation gene 3 (LAG3) that are essential for the development of self-tolerance (319). In addition, the negative regulatory checkpoint receptors can be dysregulated by cancer cells to suppress anti-tumor activity of immune response (319). CTLA4 regulates the magnitude of T cells activation during the initial stage of the immune response. Indeed, CTLA4 expression on the membrane of T cells reduces their activation by competing with CD28 in the binding with B7.1 and B7.2 in addition to provide inhibitory signals to T cells, thus activating the immune suppressive functions of Tregs (319). On the other hand, PD1 reduces the activation of T cells in peripheral tissue by directly interfering with T cell receptor signaling and restricts autoimmune phenomena (320). Cancer cells expressing PD1 ligands (PDL1 and PDL2) lead to T cells exhaustion or anergy (319, 320). In addition, PD1 is expressed by B and NK cells (321). The upregulation of PD1 ligands on cancer cells may be constitutive due to tumor cells abnormal signaling pathways activation and may lead to innate immune resistance or may mirror cancer cells adaptation to the anti-tumor response thus leading to adaptive immune resistance (319). Accordingly, CTLA4 (ipilimumab), PD1 (nivolumab and pembrolizumab) and PD-L1 antibodies were employed in clinical trials in patients with a variety of tumor types showing a clinical response (321, 322). Of note, two phase III clinical trials employing the ipilimumab have shown improved survival of patients with advanced melanoma (321). Nivolumab treatment of metastatic melanoma patients induced an objective response rate of 40% and overall survival rate of 72.9% as compared to an objective response rate of 13.9% and overall survival rate of 42.1% obtained with dacarbazine chemotherapy (321). Since the mechanisms of CTLA4 and PD1 are distinct, combined treatment with both antibodies CTLA4 and PD1 were employed (321). A Phase I clinical trial conducted in patients with advanced melanoma, showed that concurrent therapy with nivolumab and ipilimumab induced rapid and deep tumor regression in a substantial proportion of patients which appears to be distinct from that observed employing single therapy (323). Recently an anti-PDL1 monoclonal antibody, avelumab, was proven to block PD1/PDL1 interaction, to mediate ADCC of cancer cells (324). In addition, a phase I study reported its non toxicity (324).

Other clinical trials are ongoing to evaluate the efficacy of combination therapies by using anti-CTLA4 or anti-PD1 antibodies and epacadostat, an IDO1 enzyme inhibitor. Indeed, IDO1 is an intracellular immunoregolatory enzyme involved in tumor escape, tolerance and immunosuppression. IDO-expression has been identified as a prognostic marker of survival in several cancers and IDO upregulation is a critical mechanism of resistance to anti-cancer immunotherapy with CTLA4 antibodies. It has been recently demonstrated that epacadostat was able to increase dendritic cells antigen presentation, to

decrease Tregs proliferation and to increase CTLs activity. Thus the combined therapies by using an inhibitor of IDO1 represent a promising strategy in cancer immunotherapy (325).

On the other hand, the blockade of immune-checkpoint receptors by antibodies induces inflammatory adverse effects that mimic an autoimmune response (320). A patient with advanced mucosal melanoma who received four doses of a fully human monoclonal antibody against PD1 (MK-3475) had a durable near-complete response but developed severe hypothyroidism, rhabdomyolysis, and acute kidney injury (326). Therapy with a combination of ipilimumab and nivolumab, was associated with a 22% incidence of either thyroiditis or hypothyroidism and a 9% incidence of hypophysitis in melanoma patients (327). Michot *et al.* reviewed the immune-related adverse events (IRAE) found in cancer patient after immune-checkpoint receptors blockade (328). The authors reported that skin immune-related event especially vitiligo is the most frequent IRAE after blockade of the immune-checkpoint receptors in patients with melanoma. Other dermatological reactions encompassed rash/erythema and toxic epidermal necrosis (328). A small percentage (5%) of patients declared dry mouth and showed the presence of ANAs. Diarrhoea was developed in about 30% of the patients after anti-CTLA4 therapy while colitis after the same treatment resembled the characteristic of Crohn's disease. In addition, by reviewing the literature they found that some patients (5-10%) receiving antibodies to immune-checkpoint receptor developed endocrine diseases such as thyroid dysfunctiosn and hypophysitis for a deficient release of ACTH, TSH, FSH, LH, growth hormone or prolactin (328). IRAE might be also characterized by autoimmune hepatitis, immune-related- and organizing inflammatory-pneumonitis. Ophthalmological IRAEs (episcleritis, conjunctivitis, uveitis, etc) and neurological syndromes (posterior reversible encephalopathy, transverse myelitis, Guillan Barré syndrome, etc) have been described in patients receiving anti-CTLA4 antibodies (328). The presence of ANAs and anti-CCP autoantibodies characterized IRAE such as polyarthritis in patients after anti-CTLA4 therapy. Renal and pancreatic disorders were also seen in a small percentage of CTLA4 and PD1 antibodies-treated patients. Finally, hematological disorders including autoimmune neutropenia or pancytopenia, red cells aplasia have been described after patients anti-CTLA4 therapy (328). The authors concluded that the dysimmune toxicity might be associated with the antitumor response in cancer patients (328).

The value of Tregs dysfunction in generating an immune response has been consolidated in patients with paraneoplastic syndromes while the increase of Tregs has been associated with poor prognosis in cancer patients (329). Zhang *et al*. reported that patients with paraneoplastic neurological syndrome, anti-Hu autoantibodies and SCLC showed lymphopenia of CD3+ and CD4+ T cells, increased proportions of total activated T cells and activated CD4+ T cells, and reduced numbers of Tregs (329). Tani *et al*. found that the expression levels of FOXP3, TGF-β and CTLA4 mRNA in Treg-rich subsets of paraneoplastic neurological syndrome patients were down-regulated compared with that of SCLC patients without paraneoplastic neurological syndrome (330). Wang *et al.* showed that Treg infiltration was an indicator of a poorer prognosis for breast cancer patients (331). Higher Tregs frequencies were observed in early phase of bladder cancer growth and in larger tumors with more aggressive type of invasion (332). A strong immunosuppressive microenvironment in metastatic lymph nodes from patients with cervical cancer with high Tregs levels, low CD8+ T cell/Tregs ratio, and high levels of PD-L1+ and HLA-DR+-myeloid cells was reported by Heeren *et al.* (333). Therefore, immune suppression through Tregs or other types of suppressive cells resident within the tumor microenvironment, appears to be a major mechanism of tumor immune escape (334).

The association between autoimmunity, immune response to self antigens in cancer patients and anti-tumor effects obtained targeting Tregs in cancer patients is disclosed by the dysfunction of Tregs observed in patients developing autoimmune diseases (335). Tregs dysfunctions including loss of Foxp3 expression (exTreg), self-skewed TCR repertoire and atypical Treg functions including the expression of vascular endothelial growth factor or expression of RANKL have been shown to turn in pathogenic Tregs in several disease models (335). The alteration of Tregs is a key pathogenic occurrence which induces a multi-organ autoimmunity that characterizes the immune dysregulation, polyendocrinopathy, enteropathy and X-linked (IPEX) syndrome (336). Tregs alterations may lead to melanocyte loss in vitiligo, rheumatoid arthritis, type 1 diabetes and autoimmune thyroiditis (337-340) (Figure 1).

In view of all these findings, the biological activity of antibodies observed in cancer patients showing paraneoplastic syndrome might resemble the activation of immune response in cancer patients in the absence of immunosuppression. Indeed, the IRAE observed after immune-checkpoint receptors antibodies therapy might reflect a humoral and cell-mediated antitumor response.

9. CONCLUSIONS

Several studies have shown that cancer patients develop autoantibodies to self antigens with higher prevalence than healthy donor or patients

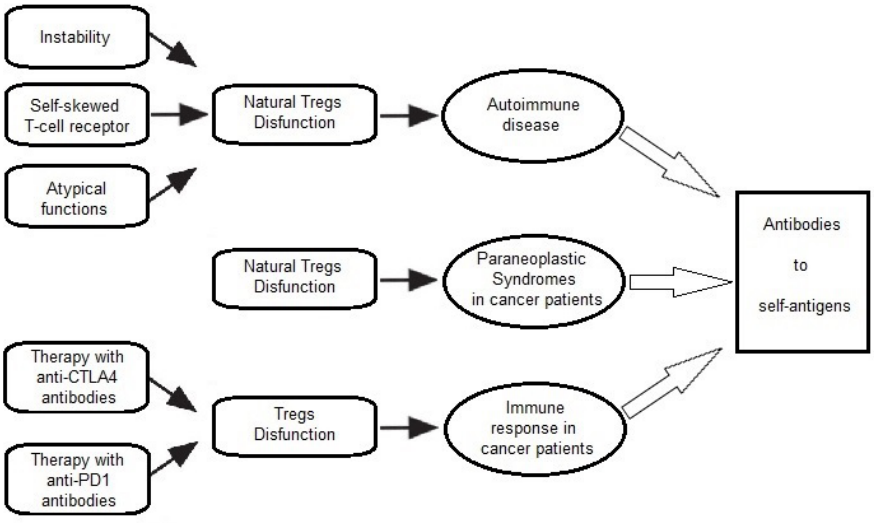

Figure 1. Disfunction of Tregs in autoimmune diseases, paraneoplastic syndromes and cancer.

with inflammatory disease. The repertoire of cancer patients autoantibodies in part overlaps that of autoimmune disease patients. Overall, the occurrence of autoantibodies is not followed by a better survival of cancer patients. However, the tumor-targeting autoantibodies induced in cancer patients deal with the immunosuppressive milieu in which they are developed and in which they would trigger their biological effects. On the other hand, autoimmune disorders often develop after alterations of tolerance checkpoints which induce Tregs dysfunctions and drive towards pro-inflammatory responses. Due to these different immunological microenvironments, autoantibodies with similar specificities may have different effects in cancer and autoimmune disease patients. Biological activities of autoantibodies to self antigens may induce paraneoplastic syndrome in cancer patients which might reflect the attempt of the patients to counteract the tumor growth. Recent studies have shown that patients with paraneoplastic syndrome have a spontaneous regression of tumors. The value of Tregs dysfunction in generating an immune response has been consolidated in patients with paraneoplastic syndromes while the increase of Tregs has been associated with poor prognosis in cancer patients. Accordingly, novel therapies have employed antibodies which target Tregs immune-checkpoint receptors. Encouraging results have been obtained following such therapy in cancer patients. The blockade of immune-checkpoint receptors by antibodies in cancer induces inflammatory adverse effects that mimic an autoimmune response in absence of immunosuppression.

Overall, the biological activities of autoantibodies in cancer might depend on their specificity, on their immunological properties and on the presence of a favorable microenvironment. Autoantibodies found in cancer patients can be used as tool for the diagnosis of cancer.

The current knowledge on the spontaneous humoral responses occurring in cancer patients, on the mechanisms that trigger self antigens autoantibodies and on the mechanisms of their biological activities might help to furnish a rationale to design anti-cancer immunotherapeutic protocols.

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Abbreviations: Treg: regulatory T cell; MHC: Major histocompatibility complex; Jo-1: Istidil-tRNA sintetasi; Sm: Smith antigens; snRNP: Small nuclear ribonucleoproteins; SLE: Systemic lupus erithematosus; RA: Rheumatoid arthritis; eIF-4G: Eukaryotic translation initiation factor-4G; CCP:

Cyclic citrullinated peptide; RF: Rheumatoid factor; ASMA: Anti-smooth muscle antibodies; TPO: Thyroid peroxidase; TG: Thyroglobulin; TSH-R: Thyroid stimulating hormone receptor; ECM: extracellular matrix; HSP: Heat shock protein; GRP78: Glucose-regulated protein 78; HCC: Hepatocellular carcinoma; GAD: Glutamic acid decarboxylase; CA II: Carbonic anhydrase II; GADPH: Glyceraldehyde 3-phosphate dehydrogenase; SOD: Superoxide dismutase; ER: Estrogen receptor; AchR: Acetylcholine receptor; VGCC: Voltage-gated calcium channels; CD20: B-lymphocyte antigen CD20; Dsg: Desmoglein; IMP: Insulin-like growth factor II mRNA-binding protein; IFN: Interferon; α_2-HSG: α_2-Heremans Schmid-glycoprotein; TCR: T-cell receptor; ANA: Anti-nuclear antibodies; CENP: centromere nuclear protein; IL: Interleukin; EGFR: Epidermal growth factor receptor; ACPA: Anti-citrullinated proteins antibody; TNF: Tumor necrosis factor; NF-κB: Nuclear factor-κB; TLR: Toll-like receptor; ANCA: Anti-neutrophil cytoplasmic antibody; ROS: Reactive oxygen species; ADCC: Antibody-dependent cellular cytotoxicity; CDC: Complement-dependent cytotoxicity; Erk: Extracellular signal-regulated kinases; Akt: Protein kinase B; PV: Pemphigus vulgaris; SCLC: Small cell lung cancer; TF: Tissue factor; VEGF: Vascular endothelial growth factor; FasR: Fas receptor; ZIC4: Zinc finger protein of cerebellum; CV2/CRMP-5: Collapsin response-mediator protein-5; mGluR1: Metabotropic glutamate receptor type 1; PCA: Purkinje cell cytoplasmic antibody; TRMP1: transient receptor potential cation channel, subfamily M, member 1; DADS: Distal acquired demyelinating symmetric; MAG: Myelin-associated glycoprotein; NMDAR: N-methyl-D-aspartate receptor; AMPAR: Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; PGA2: Polyglandular autoimmune syndrome type 2; MUC: mucin; FKBP: FK506 binding protein; PPIA: Peptidylprolyl isomerase A; PRDX: peroxiredoxin; PARP1: Poly(ADP-ribose) polymerase 1; BRCA2: Breast related cancer antigen 2; HER2: Receptor tyrosine-protein kinase erbB-2; CEA: carcinoembryonic antigen; DFS: disease-free survival; OS: overall survival; CCNY: Cyclin Y; IGFBP2: Insulin-like growth factor-binding protein 2; SMOX: spermine oxidase; NOLC1: Nucleolar and coiled-body phosphoprotein 1; MALAT1: Metastasis-associated lung adenocarcinoma transcript 1; HMMR: Hyaluronan mediated motility receptor; XAGE-1: X antigen family member-1; ADAM29: ADAM metallopeptidase domain 29; MAGEC1: MAGE family member C1; CAGE: Cancer-associated gene; BIRC: Baculoviral inhibitors of apoptosis repeat containing; CD25: Alpha chain of the IL-2 receptor; FOXP3: Forkhead box P3; CTAG: cancer/testis antigen 1; SDCCAG8: Serologically defined colon cancer antigen 8; MAPKAPK3: MAP kinase-activated protein kinase 3; ACVR2B: Activin receptor type-2B; DDX: DEAD-box protein; MUT: Methylmalonyl-CoA mutase; CSRP2: Cysteine and glycine-rich protein 2; SPOP: Speckle-type POZ protein; ZNF671: Zinc finger protein 671; ALK: Anaplastic lymphoma kinase; MSC: Mesenchymal stromal cell; TGF: Transforming growth factor; MDSC: Myeloid-derived suppressor cell; TAM: Tumor-associated macrophage; CTLA4: Cytotoxic T-lymphocyte associated protein 4; PD1: Programmed cell death protein 1; TIM3: T-cell membrane protein 3; A2aR: Adenosine A2a receptor; LAG3: Lymphocyte activation gene 3; IRAE: Immune-related adverse events; ACTH: Adrenocorticotropic hormone; FSH: follicle-stimulating hormone; LH: luteinising hormone; RANKL: Receptor activator of nuclear factor kappa-B ligand

Key Words: Tumor antigens, Autoantibodies, Paraneoplastic Syndromes, Autoimmunity, Tregs, Review

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