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Review article

Paraneoplastic antigens as biomarkers for early diagnosis of ovarian cancer

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ABSTRACT

Paraneoplastic syndromes are a group of rare disorders that can be triggered by an abnormal immune response to proteins from tumors of the lung, ovary, lymphatics, or breast. Paraneoplastic clinical syndromes affect < 1% of patients with cancer; however, the frequency of subclinical levels of paraneoplastic autoantibodies in asymptomatic patients with cancer is unknown. Numerous studies have reported that ovarian cancer patients show signs of paraneoplastic neurological syndromes (PNSs) before or after their cancers are diagnosed. PNSs arise from a tumor-elicited immune response against onconeural antigens that are shared by tissues of nervous system, muscle, and tumor cells. Studies on the serum IgGs obtained from ovarian cancer patients have indicated the presence of onconeural antibodies in the absence of any PNS symptoms. The occurrence of PNSs is low in ovarian cancer patients and it can be accompanied by onconeural antibodies. The diagnosis of PNSs is accompanied by a suspicion of a malignant tumor such that neurologists typically refer such patients for a tumor diagnostic workup. There will be tremendous utility if subclinical levels (without paraneoplastic neurological symptoms or myositis) of these autoantibodies to paraneoplastic antigens can be exploited to screen asymptomatic high-risk patients for ovarian cancer, and used as biomarkers in immunoassays for the early detection or recurrence of ovarian cancer. Ovarian cancer overall survival is likely to be improved with early detection. Therefore, a panel of onconeural antigens that can detect paraneoplastic autoantibodies in patient sera should provide diagnostic utility for an earlier therapeutic intervention. Here we review the usefulness of PNS and other paraneoplastic syndromes and their association with paraneoplastic antigens to exploit these autoantibody biomarkers to form diagnostic multi-analyte panels for early detection of ovarian cancer.

1. Introduction

1.1. Historical background of the discovery of paraneoplastic syndromes

Paraneoplastic syndromes are rare heterogeneous disorders that are characterized by the presence of endocrinological, neurological or dermatological syndromes. These disorders arise from the secretion of hormones from the tumor, or can be an autoimmune response elicited by tumor cells against onconeural antigens common to both the nervous system and to an underlying tumor (Pelosof and Gerber, 2010). The occurrence of paraneoplastic symptoms leads physicians to explore for the presence of cancer as the symptoms can appear prior to clinical manifestation of cancer. In 1825, Armand Trousseau first described the existence of a paraneoplastic syndrome called “Trousseau's Syndrome” in a gastric cancer patient who was also diagnosed with venous thrombosis. It has been reported that pancreatic, lung, and gastric cancer are associated with this syndrome, which typically appears months to years before the clinical diagnosis of a tumor (Callander and Rapaport, 1993). Hermann Oppenheim in 1888 was the first to suggest that neurological symptoms in patients with cancer could be directly connected to the underlying tumor (Schulz and Pruss, 2015). In 1912, Harvey Williams Cushing reported an endocrinological syndrome caused by a malfunction of the pituitary gland which he termed “Cushing's syndrome” (Cushing, 1994). Li et al. reported the incidence of Cushing's syndrome due to the presence of a multiple endocrine neoplasia type-1 (MEN-1) associated thymic neuroendocrine tumor (Th-NET). In 1948, Derek Ernest Denny-Brown documented a case study of two patients who had primary simple degeneration of the dorsal root ganglion cells associated with a primary degeneration of the muscles called “polymyositis”. Both of the patients who presented symptoms of severe neuropathy and ataxia had previously been diagnosed with bronchogenic pulmonary carcinoma (Denny-Brown, 1948). In 1929, Casper and in 1951, Brain et al. reported case studies that demonstrated the association of subacute cortical cerebellar

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degeneration with cancer (Brain et al., 1951). In 1968, Corsellis et al. defined “paraneoplastic limbic encephalitis” (PLE) in a study of three patients in which one patient developed memory loss that increased over a period of months and the two other patients had bronchial carcinoma associated with dementia (Corsellis et al., 1968). In 1985, Graus et al. reported the presence of neuronal antinuclear autoantibodies in four patients with subacute sensory neuropathy and small cell carcinoma of the lung (Graus et al., 1985).

The discoveries of various endocrinological, neurological and dermatological syndromes that are caused by the underlying cancer, have led neurologists to coin the term “paraneoplastic syndromes”. Paraneoplastic neurological disorders occur in the central or peripheral nervous system and can result in muscle weakness and brain degeneration, leading to immobility and death. Clinical symptoms of paraneoplastic syndromes may include loss of muscle tone, slurred speech, memory loss, vision problems, dementia, ataxia, seizures, and sensory loss in the limbs. An international panel of PNS experts has recommended consensus criteria for diagnosis of PNS (Graus et al., 2004). Paraneoplastic syndromes, if diagnosed correctly by the physician, may help to diagnose an underlying cancer before its clinical symptoms. The epidemiology of the paraneoplastic neurological disorders varies from cancer to cancer. Studies have shown that approximately 0.5–1% of all cancer patients have a clinically diagnosed PNS (Rees, 2004). This review will focus on the incidence and association of various PNSs with ovarian cancer, the pathogenesis of PNS in ovarian cancer, and the potential for onconeural antibodies to be useful tools to detect ovarian cancer at an early and potentially curable stage.

2. Incidence of paraneoplastic syndrome in ovarian cancer

Symptomatic paraneoplastic disorders are rare in patients who have gynecological cancers, and the incidence of occurrence is approximately 1 per 1000 new cases (Rees, 2004). PNSs that are most commonly associated with ovarian cancer include paraneoplastic cerebellar degeneration, dermatomyositis and polymyositis (Zahr and Baer, 2011). Women presenting with these syndromes are referred for evaluation of ovarian cancer. It has been reported that 0.1% of patients with subacute cerebellar degeneration develop ovarian carcinoma (Abrey and Dalmau, 1999). Symptoms of paraneoplastic cerebellar degeneration include ataxia, lack of balance, speech dysfunction, and nystagmus. Polymyositis is an inflammatory myopathy resulting in muscle weakness, and is associated with dermatomyositis, in which inflammation manifests in skin rashes and can co-occur with muscle weakness. Patients with either syndrome are at higher risk for malignancy.

In 1965, a survey of incidence of carcinomatous neuromyopathy in cancer patients was reported by Croft and Wilkinson. In the survey, out of 55 patients with ovarian cancer, only 9 patients were reported to have carcinomatous neuromyopathy (Croft and Wilkinson, 1965). Dalmau et al. assessed 121 neurologic consultation reports that were obtained from 83 ovarian carcinoma patients who were seen between 1993 and 1996. In that study, 38 patients were reported to develop peripheral neuropathy after the completion of chemotherapy. PNSs were observed in 4 patients; 1 patient was diagnosed with dermatomyositis and 3 patients were diagnosed with subacute cerebellar degeneration (Abrey and Dalmau, 1999). In 2010, a population based European study was reported by Giometto et al. that represented PNS association of 979 patients (968 patients had definite PNS and 11 patients had possible PNS; 899 patients had data available) recruited between 2000 and 2008 by applying the diagnostic criteria provided by Graus et al. (Graus et al., 2004). Analyses of the data that was collected from PNS Euro network database showed that 94 out of these 899 (10.5%) had ovarian cancer patients associated with a PNS (Giometto et al., 2010). In 2001, Hill et al. reported a pooled analyses of the incidence of dermatomyositis and polymyositis in cancer patients using the national data obtained from Swedish National Board of Health that spanned between 1964 and 1983, Finnish National Board of Health from 1969 to 1985, and Danish Hospital Discharge Registry from 1977 to 1989. Their study population was comprised of 618 patients with dermatomyositis, out of which 198 had cancer and 115 out of 198 patients were diagnosed with dermatomyositis prior to the cancer development. Their study showed that the standardized incidence ratio (SIR) was 10.5, at 95% confidence level (CI (6.1–18.1)) for women who developed dermatomyositis prior to diagnosis of ovarian cancer, indicating a strong association of dermatomyositis prior to symptoms of ovarian cancer (Hill et al., 2001).

3. Presentation of paraneoplastic syndromes with ovarian cancer

Numerous studies detailed the findings of PNSs with ovarian cancer. In 2000, Forgy et al. documented a case report of a patient who was diagnosed with two PNSs, nephrotic syndrome and paraneoplastic cerebellar degeneration prior to the diagnosis of ovarian cancer. CT scan and ultrasound were performed later for the evaluation of malignancy that revealed the presence of 5 cm ovarian mass and multiple paraaortic lymph nodes. Tirmzay et al. reported a case history of a 75-year old woman with stage III serous ovarian carcinoma who developed peripheral mixed sensory and motor neuropathy after surgery and chemotherapy. Eleven months after her last chemotherapy, the PNSs persisted. She developed ataxia and pseudoathetosis beside other prevailing PNSs (Tirmazy et al., 2014). Li et al. presented a case study of a 37-year old woman who developed paraneoplastic cerebellar degeneration and limbic encephalitis following Hepatitis-B vaccination. The symptoms included ataxia, slurred speech, involuntary movements of arms, depression, aggressive behavior, dysphagia and hypomnesia. The occurrence of paraneoplastic Yo antibodies were confirmed in both CSF and serum with a concurrent serum CA125 highly elevated at 2752 U/ml. The patient was diagnosed with high-grade, stage IIIc ovarian serous papillary cystadenocarcinoma. After the completion of chemotherapy and cyto-reductive surgery no ovarian cancer recurrence was observed after 38 months from diagnosis (Li et al., 2015). Hong et al. reported a case study of a 48-year old patient who had multiple erythematous skin rashes on her face, forehead, knuckles and anterior chest area. Bilateral knuckles were found to have Gottron's papules with impairment of her speech and hearing as well as weakness in muscular strength around her shoulders and leg with concurrent increased levels of aspartate aminotransferase (148 IU/l), alanine aminotransferase (130 IU/l), total creatine kinase (1190 U/l) and CA125 (543 IU/ml). The patient was diagnosed with dermatomyositis. Based on transvaginal ultrasound and MRI, the patient underwent optimal debulking, total hysterectomy and bilateral salpingo-oophorectomy due to the presence of stage IIIc high grade ovarian serous carcinoma. After the surgery, all PNSs disappeared (Hong et al., 2015). Scholz et al. reported a case study of a 45-year old woman who had problem walking because of the development of generalized shivers. She was diagnosed with opsoclonus, associated with conjugated eyes that showed movement arrhythmically in all directions. Myoclonic speech associated with dysarthria was noted. PNSs, such as truncal ataxia and limb ataxia were also observed with elevated levels of carcinoembryonic antigen (5 ng/ml) and CA125 (2161 units/ml). The presence of tumors on both her right and left ovaries was confirmed after an abdominal CT and laparotomy with a diagnosis of stage IIIc ovarian carcinoma (Scholz et al., n.d.). Appearance of Cushing syndrome in a 61-year old woman prior to the diagnosis of ovarian cancer has been reported. Two-site immunoradiometric assay (IRMA) was performed to measure the levels of Adreno corticotropic hormone (ACTH) and its precursors with blood serum and urine analysis revealing the elevated CA125 level (214.6 U/ml) and cortisol level (496 nmol/24 h). Pelvic ultrasound followed by laparotomy confirmed the presence of multicystic right ovarian mass confirmed at surgical resection as ovarian carcinoma. Hydrocortisone treatment followed by chemotherapy resulted in a long disease free interval as indicated by her post 4 years of follow-up (Al Ojaimi, 2014).

In another case study, a 60-year old woman was first diagnosed with serous ovarian cancer and later developed paraneoplastic syndrome, Acrokeratosis paraneoplastica. Ovarian cancer was suggested by an abdominal CT scan and by the rise in CA125 value (305 U/ml). Before undergoing surgery, she also developed laminar hyperkeratosis on both of her feet as confirmed by physical examination and punch biopsy of her skin (Hempen et al., 2015). Masui et al. reported the diagnosis of paraneoplastic Trousseau's syndrome in a 46-year old woman who had ovarian cancer. The patient presented multiple infarctions in her right brain, pulmonary embolism and deep vein thromboses in the area of right renal infarctions (Saho et al., 2014). Zivaljevic et al. reported a case study of a 50-year old woman who was suffering from muscle weakness and pain in her arms and shoulders. She was diagnosed with Eaton-Lambert syndrome. Treatments for PNS greatly improved her condition. She was later diagnosed with ovarian cancer (Zivaljevic et al., 2005). In 2015, Batycka-Baran et al. reported a case study of a 70-year old woman who was suffering from a very rare paraneoplastic syndrome called, erythema annulare centrifugum, for 3 years as revealed by erythematous lesions on the upper regions of thighs. She also had a history of colon cancer but did not have recurrence after surgery followed by chemotherapeutic treatments. Further blood tests revealed elevation of CA125 level and the reports from transvaginal ultrasound indicated the presence of cystic tumor on the left ovary that was later confirmed as serous papillary adenocarcinoma G2 by histological examination. After the surgery was performed, her skin lesions resolved (Batycka-Baran et al., 2015).

As paraneoplastic symptoms occur long before the diagnosis of cancer, accurate diagnosis of specific type of paraneoplastic syndrome by a neurologist can provide an indication of ovarian cancer. Further confirmation of the ovarian cancer diagnosis come from transvaginal ultrasound, abdominal PET-CT scan followed by blood test for detecting levels of CA125, as well as both blood and CSF for testing for the presence of specific onconeural antibodies. A precise diagnosis of paraneoplastic syndrome can be extremely beneficial for early detection of ovarian cancer that might be helpful in initiating antineoplastic treatments, overall survival and paraneoplastic syndrome management.

4. PNS pathogenesis in ovarian cancer

The development of PNS is commonly a result of autoimmunity. The tumor associated antigens (TAAs) can elicit an immune response to onconeural antigens expressed in certain normal tissues, such as neuronal or muscle tissues breaking immune tolerance and resulting in autoimmunity. Only a fraction of tumor-bearing patients with elevated titers of paraneoplastic autoantibodies will develop PNS. Paraneoplastic onconeural antigens are shared by nervous tissues and ovarian tumors. The pathogenesis of myositis is reported to be mediated by cytotoxic T-cells, as evidenced by an infiltration of CD8 + T-cells in the muscle of myositis patients, which are recruited by local inflammation (Carstens and Schmidt, 2014). Dermatomyositis symptoms are caused by immune-complexes binding to endothelial cells, activating the complement system and resulting in cell lysis and capillary destruction through the membrane attack complex (Carstens and Schmidt, 2014). Darnell et al. reported that the tumor-specific expression of CDR2 in neurologically normal patients with ovarian cancer. In this study, tumor specimen lysates were prepared from 20 ovarian cancer patients were probed with sera obtained from paraneoplastic cerebellar degeneration patients on western blot and 13/20 tumor lysates showed the expression of CDR2 (Yo protein) both in cerebellar neuronal tissue and ovarian tumors (Darnell et al., 2000). Expression of CDR2 was also observed in ovarian cancer patients who had no clinical manifestation of paraneoplastic cerebellar degeneration or circulating anti-Yo antibodies (Darnell et al., 2000). Therefore, the expression of onconeural antigens and their association with their respective antibodies does not always associate with the appearance of PNS (Darnell et al., 2000). Cross-reactivity of tumor and nervous tissue alone is insufficient to cause a PNS and other factors are necessary in PNS development including enhanced cytokine production, increased MHC-1 expression, and infiltration of $CD8^+$ T-cells to the tissue site (Dalakas, 2004). The occurrence of antibodies in serum and cerebrospinal fluid (CSF) that recognize the antigens shared by neurons and tumor cells has been reported. Symptoms directly resulting from antibody effects can be caused by additional antigen targets located extracellularly on the cell membrane. For example, CDR2L (a member of CDR family) has 50% sequence homology to CDR2 and its expression has been observed in both ovarian tissue and cerebellar Purkinje cells. Eichler et al. has reported that in a study population comprising patients with ovarian cancer, breast cancer and PNS patients with Yo-positive antibodies, those patients who had paraneoplastic cerebellar degeneration, harbored antibodies directed against both CDR2 and CDR2L (Eichler et al., 2013). For cytoplasmic antigens, PNS development has been reported to be T-cell mediated as directly demonstrated by detection of paraneoplastic Yo antigen specific cytotoxic T-cells in the blood sample of patient with paraneoplastic cerebellar degeneration (Albert et al., 1998).

5. Clinical use of paraneoplastic syndrome associated antibodies for diagnosis of ovarian cancer

Onconeural antibodies are more important in the diagnosis and management of PNS. These antibodies are often specific for the PNS-associated malignancy rather than for a particular neurological syndrome. Multiple antibodies may coexist in a given cancer patient. While investigating a patient for suspected PNS, the entire range of onconeural antibodies should be analyzed for proper diagnosis. As the immune system is implicated in PNSs, autoantibodies detected in patient sera may represent reliable diagnostic analytes. While a significant portion of patients with PNSs will have an underlying tumor, a small fraction of tumor-bearing patients has PNS. However, the absence of a PNS does not signify an absence of paraneoplastic autoantibodies. Cancer patients without PNS can harbor detectable onconeural antibodies, although at a lower titer than those patients presenting with a PNS. Therefore, paraneoplastic antibodies represent a stable analyte for the early detection of ovarian cancer. Numerous reports have documented the presence of different onconeural antibodies in ovarian cancer patients which are listed in Table 1.

5.1. Paraneoplastic cerebellar degeneration, paraneoplastic encephalomyeloneuropathy and encephalomyelitis-associated onconeural antibodies in ovarian cancer

Yo antibody is also known as Purkinje cell cytoplasmic antibody type 1 (PCA-1), is targeted against CDR2 antigen that has been shown to be expressed in both tumor cells and Purkinje cells, and is likewise associated with ovarian cancer and paraneoplastic cerebellar degeneration. Monstad et al. determined the prevalence of Yo antibodies in a study population comprising 557 ovarian cancer patients and 253 breast cancer patients, few of which were associated with PNS. The frequency of Yo antibody association with ovarian cancer was found to be 13/557 (2.3%), as opposed to 4/253 (1.6%) patients with breast cancer. Only 2/13 ovarian cancer patients had paraneoplastic cerebellar degeneration prior to diagnosis of ovarian cancer (Monstad et al., 2006). For paraneoplastic autoantibodies to be clinically useful for ovarian cancer diagnostics, panels of multiple antibodies will need to be employed. Karasnoudis et al. reported a case study of a 60-year patient who initially had paraneoplastic cerebellar degeneration. After performing paraneoplastic antibody screening, only Zic4 antibody titer in serum was found to be elevated. CSF also showed presence of Zic-4 antibodies. Thoracic and abdominal CT scans revealed the presence of a tumor in the right ovary and diagnosis of ovarian adenocarcinoma was confirmed (Kerasnoudis et al., 2011). Hoftberger et al. reported the appearance of carbonic anhydrase-related protein VIII (CARP VIII)

Table 1
Functions of paraneoplastic antigens that caused the generation of onconeural autoantibodies in paraneoplastic syndrome-associated ovarian cancer.

Paraneoplastic syndrome in association with ovarian cancer	Onconeural antibodies targeting paraneoplastic antigens in PNS-associated ovarian cancer	Function of paraneoplastic antigens that elicit immune responses to generate onconeural antibodies	NCBI reference sequence accession number	References
Paraneoplastic cerebellar degeneration	Yo antibody or Purkinje cell cytoplasmic antibody type 1 (PCA-1) targets CDR2 antigen	CDR2 interacts with c-myc and downregulates c-myc dependent transcription in tumor cells. CDR2 is involved in mitotic cell division.	NM_001802	O'Donovan et al. (2010); Takanaga et al. (1998)
Paraneoplastic cerebellar degeneration	Zic-4 antibodies	Zic proteins are transcription factors that have zinc finger domains that bind DNA of the target genes to regulate their transcription activity. The expression of these genes occurs during the development of cerebellum.	BC136339	Houtmeyers et al. (2013); Kerasnoudis et al. (2011)
Paraneoplastic cerebellar degeneration	Carbonic anhydrase-related protein VIII (CARP VIII) antibodies	CARP VIII protein is related to carbonic hydrase family but does not have catalytic activity of hydration of CO2. It is expressed in brain Purkinje cells and also in different cancers like lung and has been reported to cause proliferation and invasion of tumor cells thus resulting in tumor growth and progression.	NM_004056	Akisawa et al. (2003); Aspatwar et al. (2010)
Paraneoplastic cerebellar degeneration	Creatine kinase B (CKB) antibodies	Creatine kinase isoenzyme is highly expressed in brain. CKB is involved in reversible catalytic transfer of phosphate between creatine kinase and ATP, thus maintaining energy homeostatis in the cells.	NM_001823	Tetsuka et al. (2013)
Paraneoplastic encephalomyeloneuropathy	P/Q and N type calcium-channel antibodies	Neurotransmission is triggered by Calcium influx through P/Q and N type calcium-channel at the central and peripheral synapses.	X99897 M94172	Currie and Fox (1997); Lennon et al. (1995)
Encephalomyelitis	Amphiphysin antibodies	Amphiphysin is mostly present in the brain tissue and exist in two isomeric forms Amphiphysin 1 and 2. It binds to Dynamin 1 through its C-terminal SH3 domain that leads to synaptic vesicle endocytosis at the nerve terminals. It also has N terminal (BIN/amphiphysin/Rvs) BAR domain that helps it to sense membrane curvature and this property is important for coordinating vesicle formation and fission.	NM_001635	Yoshida et al. (2004)
Myositis	Jo-1 autoantibodies that target the Histidyl-tRNA synthetase antigen (HARS) or Jo-1 antigen	HARS catalyzes the transfer of Histidine amino acid to its cognate tRNA during protein synthesis. Hars is responsible for causing autoimmunity in antisynthetase syndrome by producing Jo-1 antibodies that undergo class switching and affinity maturation that are driven by T-cell activation which ultimately causes inflammation and tissue damage.	AAX99363.1	Raben et al. (1994); Zahr and Baer (2011)
Myositis	SRP-54 autoantibodies	Signal recognition particle 54 kDa protein, one of six subunits in the signal recognition particle ribonucleoprotein complex.	U51920.1	Hainzl et al. (2002); Suzuki et al. (2015)
Myositis, Myasthenia gravis	Cortactin antibodies	Cortactin aids in actin assembly by binding actin. It is a signaling protein involved in tumor invasion as well as cell adhesion, migration and endocytosis.	BC008799.2	Berrih-Aknin (2014)
Dermatomyositis	Tif-1 gamma (Trim33) autoantibodies or anti-p155/140	Tif1-gamma (Trim33) is a E3 ubiquitin ligase. Its function as a tumor suppressor depends on Trim33 dependent degradation of β-catenin.	NG_023287.1	Masiak et al. (2016); Xue et al. (2015)
Dermatomyositis	NXP-2 autoantibodies, or anti-MJ antibodies	NXP-2 protein is a nuclear matrix-associated protein. It plays an important role in RNA processing due to its RNA binding activity. It is involved in RNA metabolism.	NM_015358.2	Ishikawa et al. (2012); Kimura et al. (2002)
Dermatomyositis	CDR2L antibodies	The function of CDR2L is currently unknown. It is a paralog of CDR2 with 50% sequence homology.	NM_014603	Eichler et al. (2013)
Idiopathic inflammatory myopathy, Sjo¨gren's syndrome and Systemic lupus erythematosus (SLE)	Ro52 autoantibodies	Ro52 protein contains 3 motifs, namely, RING-finger motif, a B-box, and a coiled-coil domain and so it belongs to tripartite motif (TRIM) family. Ro52 protein has E3-ligase activity and it's overexpression in B cells reduces cell proliferation and causes an increase in apoptotic cell death.	NM_003141.3	Espinosa et al. (2006); Rutjes et al. (1997)
Antiphospholipid antibody syndrome	Phospholipid antibodies	Phospholipids can form lipid bilayers that are major components of cells. Different enzymes act on phospholipids to form secondary products that act as a second messenger in signal transduction pathways. In prostaglandin signaling pathways, phospholipids act as a prostaglandin precursor substrate for lipase enzyme.	N/A	Lands and Samuelsson (1968); Ruffatti et al. (1994)
No association of ovarian cancer with paraneoplastic syndrome	Ri antibodies bind to Nova-1 (neuro-oncological ventral antigen-1)	Nova-1, also called paraneoplastic opsoclonus-myoclonus ataxia (POMA) antigen. is a sequence specific RNA binding protein that is involved in the splicing of neuronal pre-mRNA.	NM_002515	Drlicek et al. (1997); Jensen et al. (2000)

Table 1 provides a brief description of various paraneoplastic antigens that are capable of eliciting immune responses in ovarian cancer that may be associated with different paraneoplastic syndromes. Different functions of these paraneoplastic antigens along with their NCBI reference sequence accession numbers are also listed in Table 1.

antibodies in association with paraneoplastic cerebellar degeneration at the time of ovarian adenocarcinoma tumor recurrence in a 69-year woman (Hoftberger et al., 2014). CARP VIII protein is expressed in the brain Purkinje cells, however strong expression of CARP VIII protein has been observed in lung cancer and has been linked to its higher proliferative and invasive properties that are essential for tumor growth and progression (Akisawa et al., 2003). Lennon et al. investigated the frequency of anti-P/Q and N type calcium-channel antibodies in a study population of cancer patients. Of 70 small-cell lung, ovarian or breast carcinoma patients who were associated with a paraneoplastic encephalomyeloneuropathy, 2/19 (5%) ovarian cancer patients were reported to harbor antibodies against P/Q-type and N-type calcium channels. The calcium channel antibodies were detected in human cerebellar and cerebral cortical tissues (Lennon et al., 1995). Antoine et al. reported the occurrence of amphiphysin antibodies in ovarian cancer patients in a study comprised of 2800 patients but only 5 were selected after pre-screening the sera for the presence of amphiphysin antibodies. Among 5 patients, who were diagnosed with encephalomyelitis prior to ovarian cancer diagnosis, one was found to have circulating amphiphysin antibodies (Antoine et al., 1999).

5.2. Myositis-associated onconeural antibodies in ovarian cancer

Dermatomyositis and polymyositis are paraneoplastic syndromes that can occur together or alone and symptoms can be followed by a diagnosis of ovarian cancer. The Jo-1 autoantibody that recognizes the Histidyl-tRNA synthetase is an antibody specific to myositis (Zahr and Baer, 2011). Chatterjee et al. have independently identified an epitope of the anti-Jo-1 target, Histidyl-tRNA synthetase, through a phage-display screening of serum IgGs obtained from ovarian cancer patients. This epitope, when combined in a panel of 3 antigens, had the ability to predict ovarian cancer recurrence 9 months prior to the standard clinical recurrence criteria including CA-125 (Chatterjee et al., 2012). Other autoantibodies found in the serum of myositis patients include anti-Ro52, anti-PL-7, anti-PL-12, anti-Mi-2, anti-PM-Scl75, anti-PM-Scl100, and anti-Ku (Cruellas et al., 2013). Patients with inflammatory myopathies that are positive for anti-Jo-1 are often positive for anti-Ro52. In one study examining the sera of 112 patients with inflammatory myopathies, 21% of patients were anti-Jo-1 positive, 20% of patients were anti-Ro52 positive, and 58% of those anti-Jo-1 positive patients were also positive for anti-Ro52 (Rutjes et al., 1997). In a study of 89 anti-Jo-1 positive patients with antisynthetase syndromes including polymyositis and dermatomyositis, 36 were also Ro52 positive. It was also found that when Jo-1 and Ro52 antibodies co-occurred, the risk of malignancy was associated with malignancies reported of colon, breast, ovarian, and esophagus (Marie et al., 2012). Therefore, these two antigens together on a panel could increase cancer diagnostic specificity of an autoantibody classifier. Screening of high grade serous ovarian carcinoma (HGSOC) sera was performed on diagnostic myositis antigen line blots (Mi-2, Ku, PM-Scl100, PM-Scl75, Jo-1, SRP, PL-7, PL-12, EJ, OJ, Ro-52; Ravo PNS Blot, Ravo Diagnostika, Freiburg, Germany) and on general paraneoplastic diagnostic line blots (GAD62, SOX1, Ma2, Ma1, Amphiphysin, CRMP5, Ri, Yo, HuD; Euroimmun myositis profile, Euroimmun US, Mountain Lakes, NJ). Reactivity was found with 15/20 antigens in HGSOC patient sera (Hurley et al. unpublished data). Furthermore, this onconeural autoantibody reactivity was observed in patients' serum samples drawn at times when they had CA125 values below the clinical cutoff value, 35 U/ml (Chatterjee et al. unpublished data). Additionally, reactivity of multiple paraneoplastic antigens including anti-Jo-1, anti-Yo and anti-Ro52, was observed with serum IgGs obtained from single patients. Jo-1 positive ovarian cancer patient sera with co-occurrence of Ro52 autoantibodies were observed by screening of paraneoplastic syndrome patient sera and ovarian cancer patient sera against paraneoplastic diagnostic line blots and western blot screening with recombinant full-length proteins (Chatterjee et al. unpublished data). Ishikawa et al. reported a study of screening of patients with connective tissue disease including myositis and dermatomyositis for the detection of autoantibodies that target nuclear matrix protein 2 (NXP-2). Out of 206 patients screened, 6 were positive for NXP-2. The study showed that 1 out of these 6 patients had dermatomyositis diagnosed at the same time as diagnosis of ovarian cancer. The patient was negative for antibodies to transcription intermediary factor -1gamma (Tif1-gamma) but positive for antibodies to NXP-2 (Ishikawa et al., 2012). In another study of patients with inflammatory myopathies screened against an inflammatory myopathy immunoprofile test, 11/80 patients tested positive for an inflammatory myopathy associated antibody, and 5/11 of those patients had a cancer. Out of these 5 cancer cases with positive inflammatory myopathy immunoprofiles, 1 of the cases was a woman with ovarian cancer who tested positive for Tif1-gamma (Masiak et al., 2016). Fiorentino et al. reported that in a cohort of 111 patients at the Stanford University Dermatology Clinic and a cohort of 102 patients at the Johns Hopkins Myositis Center, positivity to either NXP-2 or Tif1-gamma was present in 83% of patients with Cancer-Associated Dermatomyositis (Fiorentino et al., 2013). Suzuki et al. reported the presence of anti-SRP54 antibodies in 100 patients who had an inflammatory myopathy, 5 of whom had a malignancy, including 1 ovarian cancer (Suzuki et al., 2015).

5.3. Occurrence of autoantibodies in ovarian cancer with or without the association of other paraneoplastic syndromes

Appearance of onconeural autoantibodies has been reported in ovarian cancer in association with other paraneoplastic neurological disorders. One case study was reported of a 76-year woman who had symptoms such as, agitation, symptoms of depersonalization, and visual hallucinations that was later diagnosed as paraneoplastic Trigeminal Neuralgia using magnetic resonance imaging (MRI) and electroencephalography (EEG). After performing paraneoplastic screening test for the presence of onconeural antibodies, only Hu antibodies were shown to be present in her serum. Chest and abdominal CT scan revealed a large mass on her left ovary classified as ovarian intestinal-type mucinous tumor after the surgery (Kalanie et al., 2014). An initial diagnosis of antiphospholipid antibody syndrome (APS) in a 41-year old woman resulted in a clinical manifestation of thromboembolism (paraneoplastic in nature) with the appearance of anti-phospholipid antibodies resulting from an ovarian endometrial adenocarcinoma. The symptoms of APS disappeared after the surgical removed of the tumor (Ruffatti et al., 1994). In some cases, onconeural antibodies appeared without the development of paraneoplastic syndromes in ovarian cancer patients. Drlicek et al. investigated the prevalence of Ri autoantibodies in ovarian cancer patients that bind to Nova-1 (neuro-oncological ventral antigen-1), a neuronal antigen that takes part in splicing of pre-messenger RNA. Immunoscreening of 300 serum samples obtained from 181 ovarian cancer patients using immunofluorescence technique followed by immunoblotting indicated that 11/181 ovarian cancer patients had anti-neuronal antibodies, of which, 4/11 patients had anti-Yo antibodies and 7/11 patients had anti-Ri antibodies. The range of the titers was 1:400–1:204,800. Follow-up of all these patients indicated no development any PNSs within 2 years of their initial diagnosis. Thus, the occurrence of onconeural antibodies in ovarian cancer patients is not always accompanied by the development of PNSs (Drlicek et al., 1997).

5.4. Occurrence of onconeural autoantibodies in recurrent ovarian cancer

In addition to early detection, paraneoplastic autoantibodies can also indicate tumor recurrence and can be considered as biomarkers for disease monitoring during the patient follow up. It has been reported that return of symptoms of a PNS symptoms after successful treatment of the tumor can indicate tumor recurrence (Zahr and Baer, 2011). The titer of a paraneoplastic antibody against Ma-2 to act as a sensitive and specific predictor of recurrence has been demonstrated in small

intestine neuroendocrine tumor cancer patients (Cui et al., 2010). A case report by Forgy et al. revealed that an ovarian cancer patient developed paraneoplastic cerebellar degeneration symptoms at seven months post-surgery despite the fact that her CT scan report, CA125 levels, and physical examinations indicated no recurrence of ovarian cancer, yet her levels of Yo antibodies in the serum and in the CSF were both > 320 U/ml (normal range is < 10 U/ml) (Forgy et al., 2001). One of the early diagnostic ovarian cancer biomarkers reported by Chatterjee et al. showed amino acid sequence identity with a portion of the known paraneoplastic antigen Histidyl-tRNA synthetase, also known as Jo-1 (Chatterjee et al., 2006). This marker is one of the 3 biomarkers that predicted ovarian cancer recurrence 9 months before the confirmation of clinical recurrence when the level of CA125 was below the threshold (35 U/ml). The assay for prediction of early recurrence of ovarian cancer had an average sensitivity, specificity, and accuracy of 94.7%, 86.7%, and 93.3% respectively (Chatterjee et al., 2012).

5.5. Novel paraneoplastic antigens with myositis and paraneoplastic cerebellar degeneration associated ovarian cancer

Although paraneoplastic antibodies known to be associated with cancer have been studied in detail, the search for new paraneoplastic cancer associated autoantibodies is ongoing. Two recent findings include antibodies to cortactin and creatine kinase brain type (CKB) (Berrih-Aknin, 2014; Tetsuka et al., 2013). Cortactin was recently identified as a paraneoplastic antigen in two independent studies (Berrih-Aknin, 2014). Following identification, both groups screened paraneoplastic sera against cortactin; one group detected cortactin antibodies in 20% of polymyositis patients using ELISA with western blot confirmation, while the other group identified cortactin antibodies in 19.7% of myasthenia gravis patients who were sero-negative for classic paraneoplastic antigens (Berrih-Aknin, 2014). Myositis is a PNS closely linked with ovarian cancer. Cortactin has been reported to be overexpressed in ovarian cancer by mRNA analysis of tumor tissues as well as by immunohistochemical staining of cortactin on tumor histological sections, and its expression was associated with poor prognosis (Li et al., 2016). Therefore cortactin autoantibodies can be useful biomarkers for early detection of ovarian cancer. Another recently identified paraneoplastic antigen is creatine kinase brain type, CKB. In an effort to identify novel paraneoplastic antigens in patients with cerebellar degeneration that were sero-negative for classic paraneoplastic markers, 2D western blot of paraneoplastic antibody sero-negative sera followed by mass spectrometry identified CKB as a novel paraneoplastic cerebellar degeneration-associated antigen (Tetsuka et al., 2013). CKB serum antibody reactivity was demonstrated in the cytoplasm of mice Purkinje cells as well as urinary bladder cancer tissue samples. CKB was elevated in several cancers including stage 1 ovarian cancer patients and was demonstrated to contribute to cancer progression (Li et al., 2013). CKB antibodies could provide an outstanding early stage ovarian cancer biomarker. As more paraneoplastic antigens are discovered, the panel of antigens to use for diagnosis of ovarian cancer could be expanded.

5.6. Future panels of paraneoplastic antigens on different platforms for early diagnosis of ovarian cancer

Research on the occurrence of onconeural antibodies in ovarian cancer remains ongoing. Generating a panel of paraneoplastic antigens, along with previously identified diagnostic biomarkers for ovarian cancer, could provide a screening strategy using various clinical immunoassay platforms, such as indirect immunofluorescence (IIT), immunoblotting, line-blots, multiplex luminex, ELISA, with sufficient sensitivity and a mortality benefit for early diagnosis of ovarian cancer. Cancers that are most frequently associated with PNS include SCLC, breast, and ovarian. As lung cancer is associated with PNSs, an FDA-approved ELISA based test, the EarlyCDT-Lung panel, incorporates the paraneoplastic antigens, HuD and SOX2 for the autoantibody detection of lung cancer in at-risk smokers (Jett et al., 2014).

It is well established that while single autoantibodies have low frequency of positive titer among cancer patient sera, a combination of autoantigens for detection of autoantibodies can greatly increase diagnostic sensitivity. Cui et al. reported a study where 124 sera obtained from patients diagnosed with small intestine neuroendocrine tumors (SI-NETs) were screened using recombinant Ma2 protein on ELISA platform that resulted in high sensitivity and specificity as revealed by the AUC values between 0.734 and 0.816 obtained from ROC curve analysis (Cui et al., 2010). Maat et al. developed a multiplex Luminex assay using six onconeronal antigens, namely NOVA-1 (Ri), HuD, Ma2, CDR62 (Yo), CRMP-5 (CV2), amphiphysin to immunoscreen 119 patients who had definite PNS. Their assay yielded a high sensitivity, such as 83% for Ri antigen, 91% for Ma2, 93% for HuD and 100% for Yo, CV2 and amphiphysin. High specificity was also obtained, 96% for CV2, 97% for HuD, Yo, amphiphysin, 99% for Ma2 and 100% for Ri antigens (Maat et al., 2013). As the diagnosis of paraneoplastic syndrome precedes the diagnosis of cancer, therefore, a panel of paraneoplastic antigens will have utility in the diagnosis of cancer.

Although the lifetime risk of developing ovarian cancer for a woman is 1.4%, the risk of ovarian cancer significantly increases and it ranges from 39% to 44% for women associated with BRCA1 mutations and from 12% to 20% for women carrying BRCA2 mutation (Smith, 2017). Earlier studies indicated that 50% (17/34) ovarian cancer patients harbored autoantibodies to BRCA1, 5.9% (2/34) were associated with BRCA2 autoantibodies, 29.4% (10/34) had autoantibodies to PARP, and 29.4% (1/34) women had autoantibodies to PARP and BRCA1. It was also shown that cancer patients with PARP autoantibodies were associated with paraneoplastic neurological disorder (Zhu et al., 2015). Therefore, a panel of multiple antigens could increase the sensitivity of antibody-based tumor diagnostics, and in the case of ovarian cancer, a panel including paraneoplastic antigens could serve to detect autoantibodies in high-risk populations with known deleterious BRCA1/2 mutations or family history of ovarian cancer.

6. Conclusion

The diagnosis of ovarian cancer has been challenging due to a dearth of biomarkers for sensitive and specific screening tests. Paraneoplastic neurological disorders that appear in ovarian cancer patients are considered to be remote effects of cancer and may occur in association with onconeural antibodies. Panels of paraneoplastic antigen targets of these onconeural antibodies may be useful in developing diagnostic immunoassays for early detection of ovarian cancer and its recurrence in a clinical setting.

Conflict of interest

Dr. Tainsky is a paid consultant to Avant Diagnostics on ovarian cancer biomarkers. Dr. Tainsky and Dr. Chatterjee are coinventors on patents issued and pending for autoantibody biomarkers.

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