

REVIEW

Autoimmunity and Cancer

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Abstract

The association between autoimmune diseases and cancer is to be considered one of the most well established and clinically challenging issues. Several mechanisms are shared in the pathogenesis of both autoimmune diseases and cancer, they are thus direct candidates as causative factors, but direct proof is lacking, as in the case of serum autoantibodies. Furthermore, accurate estimates of the risk of cancer in patients with newly diagnosed or long-standing autoimmune disease remain to be reported. The role of awareness bias and diagnosis latency, as well as of serum autoantibodies, epigenetics and genomic susceptibility, cannot be overlooked in this scenario. Finally, an indirect proof of associations is provided by the common autoimmune phenomena presenting as paraneoplastic. The present article will critically review the available evidence on the common mechanisms and epidemiology underlying the risk of cancer in patients with autoimmune disease.

Keywords: Autoimmunity - cancer - genetic susceptibility - epidemiology

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Introduction

The complex relationship between autoimmunity and cancer has been reported in numerous studies over the past years, based on the assumption that autoimmune disease and malignancies share several common features. First, similar patterns of immune dysregulation characterize both conditions as well represented by serum autoantibodies that can be detected not only in autoimmune but also in neoplastic disease although in the latter there is limited evidence on their pathogenetic role. Second, clinical observations suggest that autoimmunity and malignancy are linked in a bidirectional way as clinical features resembling autoimmune disease are frequently encountered in paraneoplastic syndromes. In a complementary fashion, autoimmune diseases are characterized by an increased neoplastic risk, mainly involving hematological malignancies, compared with the general population. The mechanisms underlying this susceptibility to malignancy can only be speculated and a number of hypotheses have been proposed, from genetic and environmental common features, to intrinsic properties of autoimmune disease. Finally, the possible role of immunosuppressive drugs in determining the neoplastic potential cannot be overlooked. Based on these observations, the present article was intended to provide an overview of the current evidence regarding this fascinating and somehow unsuspected association. In particular, we examined the mechanisms that link autoimmune disease to the increased risk of cancer development, evaluating the risk in major autoimmune rheumatic diseases. Of note, the complementary issue of paraneoplastic autoimmunity will not be discussed in depth.

Serum Autoantibodies in Cancer

One of the most striking observations for physicians is the positivity of serum autoantibodies in subjects affected by solid or haematological cancer which has been documented in several studies (Burnham, 1972; Wasserman et al., 1975; Imai et al., 1992; Zuber, 1992; Solans-Laque et al., 2004). Nevertheless, the mechanisms involved in these autoimmune phenomena remain enigmatic. The two major hypotheses include the enhanced expression of autoantigens by tumor cells and the ensuing of chronic inflammation in the tumor microenvironment (Coussens and Werb, 2002; Mantovani et al., 2008). A large panel of specific autoantibodies has been reported in patients with cancer and is referred to as tumor associated autoantigens (TAA). TAA are detected with numerous techniques, including ELISA panels for large numbers of autoantigens (Chapman et al., 2008) but these methods are not yet validated for clinical use and their specificity needs to be improved. Over 400 different autoantigens were identified using a serological analysis of recombinant cDNA expression libraries of human tumors with autologous serum (Old and Chen, 1998) and these were arrayed into six different categories. First, cancer/testis antigens, normally expressed in male germ cells in the testis, are found in several tumors. To date, about 20 such antigens have been isolated from different neoplastic cells, including MAGE, BAGE, CAGE, SSX and others (Scanlan et al., 2002). Second, mutational antigens normally encoded by tumor suppression genes have been identified and these frequently include the p53 protein with a prevalence of 65% described in several studies (Lubin et al., 1995; Soussi, 2000). These

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autoantibodies appear to be secondary to the strong immunogenicity of mutated forms of p53 gene (Soussi, 2000). The third category includes differentiation antigens such as melanocyte-specific protein tyrosinase (Sahin et al., 1995) and NY-BR-1 in breast cancer (Jager et al., 2001). Fourth, overexpressed genes coding for antigens are represented by cell surface receptors like HER2/neu in breast cancer, or enzymes like carbonic anhydrase XII in kidney cancer (Tureci et al., 1998), and aldolase A in lung cancer (Gure et al., 1998). A fifth group is constituted by splicing variant antigens, well represented by restin in Hodgkin's lymphoma cells (Sahin et al., 1995). Finally, human endogenous retroviruses gene products may elicit autoimmune phenomena and have been hypothesized to contribute to the susceptibility to autoimmune diseases and malignancy (Herbst et al., 1996; Herrmann et al., 1996). Of note, all data about autoantigens associated with cancer are currently collected in the Cancer Immunity databases (<http://www.cancerimmunity.org/peptide/>). T cell antigens are arrayed into two major groups, unique and shared (Table 1). Unique antigens are derived from point mutations of ubiquitous genes, like K-ras and p53, and are exclusive to single patients while shared antigens are commonly found in larger population. Within this latter group, MAGE, CAGE, tyrosinase, HER2/neu have been recognized as independent antigens (Van der Bruggen, 2012). A specific class of autoantibodies associated with cancer are directed against onconeural antigens (Hu, VGCC, Ri, Tr, and Yo), which can commonly be found in patients affected by neurological paraneoplastic syndromes. Indeed, antibodies against the Hu antigen can be found in 90% of patients affected by lung tumors, in particular of small cells variant lung tumor (Lucchinetti et al., 1998) and are associated with the "anti-Hu syndrome" characterized by encephalomyelitis, sensorial neuropathy, cerebellar degeneration, and gastrointestinal dysmotility (Benyahia et al., 1999). In the cases of anti-Yo, anti Ri, and anti-Tr antibodies, these are supposed to be associated to cerebellar degeneration (Fathallah-Shaykh et al., 1991; Drlicek et al., 1997; Graus et al., 1997).

As the most widely represented autoantibody in both health and disease, anti nuclear autoantibodies (ANA) was first reported in 1971 by Whitehouse et al. in 24% of overall neoplastic diseases and 50% of breast cancer (Whitehouse and Holborow, 1971). Further, Shield et al. (1989) observed that cancer had been diagnosed in 2.9% of the subjects who were occasionally positive for ANA (Shiel et al., 1989). More recently, a case-control study on 274 oncological patients and 140 controls demonstrated a significant prevalence (OR 8.57, 95%CI 3.6-24.6) of ANA using indirect immunofluorescence. The speckled immunofluorescence staining pattern

was the most representative type in ANA analysis but no specificity was found between ANA versus common antigens (anti-dsDNA, anti-ENA) in connective tissue diseases. These data are probably burdened by the presence of very specific antigens in patients affected by tumors (Solans-Laque et al., 2004) and several studies are now dedicated to identify novel methods to isolate more specific tumor autoantibodies. The clinical use of ANA test in the diagnosis and prognosis of cancer has been largely investigated and the presence of these autoantibodies has been hypothesized to appear up to 6 years before the diagnosis of cancer (Frenkel et al., 1998). This finding could indicate ANA as a potential biomarkers of disease, and could allow the identification of patients at risk for tumors but a prospective confirmation is awaited to recapitulate the proposed predictive value of serum ANA.

Malignancy in Autoimmune Disease

Cellular bases

It is well established that numerous factors concur and are necessary to cause the elevation of the risk of neoplasia in patients with autoimmune disease compared to the general population. For this, several pathogenetic mechanisms have been hypothesized, including genetics, environmental factors, activation of the immune system by autoantigens, and prolonged immunosuppressive treatments. Nevertheless, most of these remain speculative. Autoimmune systemic diseases carry an increased risk of non-hematological malignancies, and the association between autoimmunity and non-Hodgkin lymphoma (NHL) has gained more interest. B cell NHL represents the most frequent hematological malignancy ensuing in rheumatological diseases and its risk is greatest in patients with Sjögren syndrome (SS). This paradigmatic model of lymphomagenesis warrants a more detailed discussion. SS is characterized by the B cell attack of the exocrine glands and dysregulated expression of B cell-activating factor (BAFF) (Tapinos et al., 1999; Sellam et al., 2007; Voulgarelis and Tzioufas, 2010) following the polyclonal B cell activation leading to local production of cytokines and to increased titers of serum autoantibodies, particularly anti-Ro and anti-La. Infiltrated glands are frequently the site of B cell oligoclonal and monoclonal expansion, a condition leading to lymphoid malignancy in more than 14% of SS cases (Kassan et al., 1978; Voulgarelis et al., 2001; Guzman et al., 2010). Over the disease natural history, a large number of SS cases will develop B cell NHL, mainly mucosa-associated lymphoid tissue (MALT) lymphomas (Tzioufas et al., 1990; Voulgarelis et al., 1999; Gasparotto et al., 2003). Although the transition from a chronic inflammatory condition to malignant lymphoma

Table 1. Classification of Autoantigens Found to React with Serum Autoantibodies from Patients with Cancer (Van der Bruggen P, 2012)

Category	Mechanism	Representative antigens
Unique	<i>Point mutation of ubiquitous genes (patient-restricted)</i>	K-ras, p53
Shared	<i>Tumor-specific</i>	BAGE, CAGE, MAGE
	<i>Differentiation antigens</i>	<i>Expressed in the primary normal tissue of the neoplasia (not tumor-specific)</i> Tyrosinase, NY-BR1
	<i>Overexpressed antigens</i>	<i>Expressed in normal tissues (not tumor-specific)</i> HER2/neu, p53

is a poorly understood, multistep process similar to what observed in inflammatory bowel disease and colorectal carcinoma (Voulgarelis and Tzioufas, 2010) is supposed to be involved. There is an increasing evidence that the chronic stimulation by exogenous antigens or autoantigens plays an essential role in the development of SS associated lymphoproliferation. Additional molecular oncogenic events such as microsatellite instability, loss of the B cell cycle control, and the forced overproduction of specific B cell biologic stimulators seem to contribute to the emergence and malignant transformation (Sellam et al., 2007). The use of polymerase chain reaction (PCR) to investigate the immunoglobulin heavy chain gene clonal rearrangement allowed to demonstrate monoclonality or oligoclonality in 58% and 79% of B cells from the minor salivary glands of SS cases, respectively (Guzman et al., 2010). In this context, it is now established that the risk of NHL progression is high if these B cell clones are detected in different tissues at different times (Jordan et al., 1996). Moreover, the presence of B cell clonality in minor salivary glands can be used as an index of an altered microenvironment, which could enable the development of NHL in SS (Sellam et al., 2007). Circulating monoclonal Ig were reported using immunoelectrophoresis methods in nearly 20% of patients with primary SS (Brito-Zeron et al., 2005). Related to dysregulated B cell proliferation, CD4+ T cells and dendritic cells locally produce B-cell targeted cytokines and other survival factors, including BAFF, when a lymphoid infiltration is established in the salivary glands of patients with SS (Mariette et al., 2003). Accumulating evidence supports the importance of BAFF as an important mediator in the neogenesis of germinal centers in SS (Mariette et al., 2003) and BAFF is secreted not only by salivary epithelial cells but also by B cells, which highlights the important effect of this factor in the initiation and perpetuation of B-cell dysregulation in SS (Varin et al., 2010; Groom et al., 2002; Daridon et al., 2007). This can be demonstrated by the presence of circulating immune complexes, hypergammaglobulinemia, alterations in peripheral B cell subpopulations, oligoclonal B cell expansion and the increased risk of developing NHL. The reduced level of apoptosis among BAFF-expressing cells in the salivary glands from SS patients potentially leads to abundant BAFF expression, thereby amplifying B-cell signaling, promoting the regional proliferation of B cells and their differentiation into autoantibody-producing plasma cells (Mariette et al., 2003). In fact, plasma levels of BAFF in SS patients are strongly associated with autoantibody titers, including those of rheumatoid factor and anti-Ro/SSA (Nossent et al., 2008). These observations are of paramount importance based on the recent FDA approval of a BAFF-targeting monoclonal antibody for the treatment of SLE (Vincent et al., 2012).

Chronic lymphocytic leukemia (CLL) also represents a frequent coexisting condition in autoimmunity. CLL shares several pathogenetic features with autoimmune disease and is commonly associated to autoimmune phenomena. The presence of somatic hypermutation of Ig heavy-chain variable (IgV) allows to classify CLL into two subtypes, mutated CLL (M-CLL) and unmutated CLL (UM-CLL)

(Herve et al., 2005). In CLL the B cell receptor (BCR) profile is homogeneous, stereotyped, and independent of the IgV genotype, (Klein et al., 2001) suggesting that BCR stimulation by similar epitopes plays a pivotal role in the pathogenesis of CLL (Damle et al., 2002; Chiorazzi et al., 2005). Although the antigens remain to be identified, antigenic BCR stimulation promotes the leukemic transformation and the growth of the neoplastic clone (Chiorazzi and Ferrarini, 2003). It has been hypothesized that latent viruses or commensal bacteria, environmental antigens, and autoantigens as well, could promote and sustain the clonal expansion (Chiorazzi et al., 2005). Clonal cells often have polyreactive receptors, which recognise several antigens including autoantigens (Catera et al., 2008). Borche et al. (1990) showed that monoclonal CD5+ B cells can produce natural autoantibodies. Monoclonal autoantibodies are responsible of cold agglutinin disease and paraneoplastic pemphigus (Hodgson et al., 2011). However, other autoimmune phenomena, especially autoimmune hemolytic anemia (AIHA) and immune thrombocytopenic purpura, are also the result of polyclonal autoantibodies (Kipps and Carson, 1993; Hamblin, 2006), suggesting different mechanisms are operating for tumorigenesis and autoimmune diseases. In AIHA, CD5+ CLL cells can act as antigen presenting cells (APC), processing Rh proteins, and triggering a Th-cell response (Hall et al., 2005; Hamblin, 2006). Similarly, abnormal T cell function plays an important role in the autoimmune phenomena. This was elucidated in 1990s in that the use of purine analogs to suppress CD4+ T cells and Treg (Beyer et al., 2005) led to an increased incidence of autoimmune cytopenia (Tosti et al., 1992; Myint et al., 1995). Further studies demonstrated that, in patients without prior history of autoimmune cytopenia, the incidence is not superior in purine analogs treated group (Dearden et al., 2008). Moreno et al. analyzed the prognostic value of autoimmune cytopenia in CLL, and showed that in patients with advanced disease the immune origin of the cytopenia confers a better prognosis than the infiltrative one (Moreno et al., 2010).

Risk estimates

It is widely known that specific autoimmune diseases are characterized by an elevated risk of cancer development, as in the case of celiac disease and inflammatory bowel disease. Both of these have a well demonstrated risk of hematological and gastrointestinal malignancies development, despite their different pathogenesis and immunohistological characteristics (Molberg et al., 2003; Sartor, 2006). Askling et al. (2009) studied a cohort of over 12,000 patients and reported that adults with CD had an increased overall risk for colorectal carcinoma and other types of cancer, except for breast cancer, of which incidence appeared lower in celiac disease affected patients. In particular, the data demonstrated a standardized incidence ratio (SIR) of 10.0 (95%CI 4.4-20) for small bowel cancer, 4.2 (95%CI 1.6-9.2) for esophageal carcinoma and 6.3 for NHL (95%CI 4.2-125). Furthermore, the risk of lymphoma decreased with time of follow-up (Askling et al., 2002). Equally IBD carry a greater risk of gastrointestinal cancer and hematological

malignancy. Following over 21,000 patients affected by Crohn's disease, Hemminki et al. (2009) reported a SIR of 13.82 (95%CI 10.41-18.00) for small bowel tumors, 2.93 (95%CI 2.52-3.39) for colon cancer and 2.54 (95%CI 2.03-3.15) for NHL. The SIR decreased when excluding cases in which the diagnosis of cancer had been made during the first year. The same group demonstrated that ulcerative colitis also carries an increased risk of cancer development which can be estimated in a SIR of 3.60 (95%CI 3.23-4.00) for colon cancer, 4.30 (95%CI 3.63-5.07) for liver neoplasia, and 1.52 (95%CI 1.20-1.91) for NHL. As shown for Crohn's disease, for ulcerative colitis the relative risk also decreases after the first year of follow up (Hemminki et al., 2008a). In more general terms, both prospective and case-control studies have been conducted to establish the risk of cancer development. A large retrospective study supporting the hypothesis that chronic autoimmune syndrome can lead to lymphoid malignancy was conducted by Anderson et al. (2009) on a population of about 44,000 patients with lymphoma included in the U.S. Surveillance Epidemiology and End Results-Medicare database and 122,000 controls. As somehow expected, the strongest associations were found between diffuse large B-cell lymphoma (DLBCL) and SS (odds ratio OR 2.0, 95%CI 1.5-2.8) and rheumatoid arthritis (AR) (OR 1.4, 95%CI 1.2-1.5); marginal zone lymphoma showed a strong link with SS (OR 6.6, 95%CI 4.6-9.5) and systemic lupus erythematosus (SLE) (OR 2.8, 95%CI 1.7-4.7) while Hodgkin lymphoma (HL) was also associated with SLE (OR 3.5, 95%CI 1.9-6.7).

Sjögren's syndrome

As illustrated when mechanisms of neoplasia associations were discussed, among autoimmune diseases, SS carries the highest risk of lymphoproliferative transformation and has been largely studied as a model of lymphomagenesis through different mechanisms (Manoussakis et al., 2010; Mavragani and Crow, 2010; Roguedas et al., 2010; Kapsogeorgou et al., 2011). In 1978 described a 44 fold increased risk of lymphoma development in SS affected patients (Kassan et al., 1978). In more recent studies the reported SIR ranged from 1.9-33.3 (Kauppi et al., 1997; Soderberg et al., 2006; Theander et al., 2006; Anderson et al., 2009). In a large multicenter retrospective study, the estimated prevalence of NHL was 4.3% (95%CI 3.0-6.0) (Voulgarelis et al., 1999). The most common histopathologic type of lymphoma is MALT lymphoma, in particular marginal zone lymphoma, (Kassan et al., 1978; Royer et al., 1997; Voulgarelis et al., 1999), followed by DLBCL which can be primitive or derived from MALT lymphoma transformation (Voulgarelis and Skopouli, 2007). The salivary glands, mainly parotid glands, are the most frequently involved organs, but other sites can be affected, including the stomach, pharynx, skin, liver, kidney, and lung (Voulgarelis and Skopouli, 2007). Among the clinical and serological issues that have been associated with lymphoma development, the presence of cutaneous vasculitis, parotid gland hypertrophy, lymphadenopathy, neuropathy (Royer et al., 1997; Sutcliffe et al., 1998; Voulgarelis et al., 1999), low C4 (Voulgarelis et al., 1999; Skopouli et al., 2000), mixed

monoclonal cryoglobulinemia (Tzioufas et al., 1996; Voulgarelis et al., 1999), urinary free light chains (Walters et al., 1986), and β -2 microglobulin levels (Anaya et al., 1996) constitute the main predictive markers, and patients displaying these risk factors should be closely monitored (Anaya et al., 1996). NHL is a late complication of SS, developing from 7.5-14 years from the SS onset (Royer et al., 1997; Sutcliffe et al., 1998; Voulgarelis et al., 1999). Early non invasive markers for NHL transformation in long-standing SS are currently being sought and should be a priority for research: currently proposed markers are depicted in Table 2.

Rheumatoid arthritis

The autoimmune injury observed in RA (Tobon et al., 2010; Iobagiu et al., 2011; Somers et al., 2011) is associated with an elevated overall risk of cancer development, in particular of the lung (SIR 1.36-2.29) (Yamada et al., 2011; Hemminki et al., 2008b; Chen et al., 2011; Dreyer et al., 2012) and kidney (SIR 1.53-2.12) (Hemminki et al., 2008b; Chen et al., 2011). On the contrary, the reported incidence rates for breast (SIR 0.87-1.21) (Hemminki et al., 2008b; Gadalla et al., 2009; Chen et al., 2011), gynecological (SIR 0.66 for endometrial and 0.86 for cervix cancers) (Chen et al., 2011) and gastrointestinal cancer (SIR 0.7 for colon and 0.68 for rectal carcinoma) (Hemminki et al., 2008b) are lower than in the general population. Furthermore, RA is related to an increased risk of lymphoma development, both NHL (SIR 1.2-5.4) (Abasolo et al., 2008; Hemminki et al., 2008b; Anderson et al., 2009; Chen et al., 2011; Dreyer et al.) and HL (SIR 1.5-4.81) (Hemminki et al., 2008b; Anderson et al., 2009; Chen et al., 2011; Dreyer et al., 2012). In a cohort study of 23,644 Asian patients with RA, Chen et al. demonstrated that the incidence of lymphomas was higher in younger patients and during the first year of follow up (Chen et al., 2011). Ekstrom and colleagues also found the same time-limit lymphoma risk, having observed 76,527 patients for more than 30 years. The latter authors analyzed the risk of lymphoma in first-degree relatives, but failed to demonstrate a correlation thus possibly going against the proposed role for genomics (Ekstrom et al., 2003). Indeed, several factors have been considered to

Table 2. Proposed Clinical and Serological Predictive Markers of Lymphoma Development in SS

Clinical markers:	
-	Lymphadenopathy and splenomegaly (Sutcliffe et al., 1998; Voulgarelis et al., 1999)
-	Parotid gland hypertrophy (Sutcliffe et al., 1998; Voulgarelis et al., 1999)
-	Cutaneous vasculitis (Sutcliffe et al., 1998; Voulgarelis et al., 1999)
-	Neuropathy (Voulgarelis et al., 1999)
Serological markers:	
-	Low C4 levels (Voulgarelis et al., 1999; Skopouli et al., 2000)
-	Mixed monoclonal cryoglobulinemia (Tzioufas et al., 1996; Voulgarelis et al., 1999)
-	Urinary free light chains (Walters et al., 1986)
-	β -2 microglobulin (Anaya et al., 1996)

explain the higher risk of lymphoma in RA. Among these, Baecklund et al. focused on the inflammatory activity, and demonstrated that patient with high disease activity have a 70-fold increase in the risk of lymphoma. The same authors reported an increased risk in azathioprine treated patients, but other DMARDs including methotrexate did not seem to be a risk factor in lymphoma development (Baecklund et al., 2006).

Systemic sclerosis

Patients affected by SSc manifest several immune dysfunctions (Gourh et al., 2010; Takagi et al., 2011) and are prone not only to hematological malignancy but also to other types of cancer, particularly of the lung and esophagus, the two areas frequently involved in the fibrotic process. At the same time, SSc is one of the most common paraneoplastic syndromes and its onset can occur before, simultaneously or after cancer. The reported SIR ranges from 2.1-18.6 for lung (Kang et al., 2009; Olesen et al., 2010), and from 2.86-35.0 for esophageal cancer (Derk et al., 2006; Kang et al., 2009; Landgren et al., 2011). The described relative risk of hematological malignancies is, likewise, extremely higher, not only for NHL, SIR ranging from 2.0-25.83 (Siau et al., 2011; Mellekjær et al., 2008; Olesen et al., 2010), but also for multiple myeloma (MM) (Siau et al., 2011). Limited scleroderma, male sex, older age and a long-lasting disease appear to be the most important risk factors in cancer development (Czirjak et al., 2008; Szekanecz et al., 2008; Olesen et al., 2010). Recently, Shah et al. (2011) studied the temporal link between SSc and cancer and reported that in patients with anti RNA polymerase III antibodies cancer diagnosis was made before or within 2 years of SSc onset. This observation suggests the hypothesis that SSc-associated antigens could be cross-reactive with neoplastic cells (Shah and Rosen, 2011).

Systemic lupus erythematosus

The overall risk of cancer in a paradigmatic disease such as SLE (Kontaki and Boumpas, 2010; Fu et al., 2011) is only slightly increased, probably due to the fact that despite the higher incidence of specific malignancies, other tumors are less frequent than in general population. Hematological malignancies are predominantly incident cases with SIR ranging from 1.5-15.37 for NHL (Smedby et al., 2006; Anderson et al., 2009; Kang et al., 2010) and from 3.02-5.8 for HL (Landgren et al., 2006; Parikh-Patel et al., 2008; Anderson et al., 2009). In a multicenter cohort that included 9,547 SLE cases, Bernatsky et al. (2009) confirmed the slightly increased overall risk for cancer (SIR 1.15, 95%CI 1.05-1.27) and the significant higher risk of hematological malignancies (SIR 3.64, 95%CI 2.63-4.93). The data showed also an increased risk of lung (SIR 1.37, 95%CI 1.05-1.76) and hepatobiliary cancers (SIR 2.60, 95%CI 1.25-4.78) and decreased risks of endometrial (SIR 0.36, 95%CI 0.13-0.78), and breast cancers (SIR 0.76, 95%CI 0.60-0.95) (Bernatsky et al., 2005). The RR of hematologic malignancies and other cancers is comparable in both sexes and different ages, but seems to be greater during the first years duration of the disease (Bernatsky et al., 2005). In a different study,

the same authors reported that longer disease duration appeared to be protective (HR 0.88, 95%CI 0.82-0.93). In the same study, age over 65 (HR 2.69, 95%CI 1.38-5.24) and the presence of non-malignancy damage (HR 3.07, 95%CI 1.97-4.81) appeared to confer a greater cancer risk. On the contrary, the risk of all malignancies was not affected by the immunosuppressive treatment (Bernatsky et al., 2008). The prevalence of cancer in the first years of disease suggests that immunosuppressive treatments do not play an essential role in malignancy predisposition, but other factors, like disease activity, may indeed contribute. The clinician should thus be aware of the increased risk of lymphoma and should investigate SLE patients with symptoms like lymphadenopathy, splenomegaly, and weight loss, before accounting them as flares of the underlying autoimmune disease. Other studies reported that SLE carries a greater risk of carcinomas of the vagina/vulva (SIR from 3.27-4.76), nasopharynx (SIR 4.18), kidney (SIR 3.99) (Chen et al., 2010), liver (SIR 2.70) (Parikh-Patel et al., 2008), and lung (RR 1.73, CI 95% 1.25-2.32) (Bjornadal et al., 2002). On the contrary the risk of endometrial, breast and ovarian cancers appears to be lower than in general population (Cibere et al., 2001; Parikh-Patel et al., 2008; Chen et al., 2010). The reason for the reduced incidence of gynecological cancer may be secondary to the duration of exposure to estrogens (Bernatsky et al., 2008) related to the increased risk of premature ovarian failure, due to both primary and iatrogenic causes (Takada et al., 2001; Cooper et al., 2002). Secondly exogenous estrogens are rarely prescribed to SLE affected patients, because of the well known probability of a disease flare (Bernatsky et al., 2008). Lofstrom et al. performed a retrospective study on 16 SLE patients who developed NHL and 26 SLE patients without malignancy as controls, and reported that DLBCL is the most common subtype of lymphoma in SLE patients. The prevalence of DLBCL was 65% versus 30-40% in general population (1997). The lymphoma diagnosis had been made in a time range from 1 year to 29 years from the SLE diagnosis and some clinical features appeared related to the increase risk of lymphoma, including the presence of autoimmune hemolytic anemia (RR 3.2, 95%CI 2.0-5.0), SS-like symptoms (RR 2.7, 95%CI 1.5-5), and pulmonary involvement (RR 2.5, 95%CI 1.3-4.9). On the contrary, the RR of lymphoma was not significantly higher in immunosuppressive treated patients (RR 1.1, 95%CI 0.5-2.5) (Lofstrom et al., 2007).

Dermatomyositis and polymyositis

Both dermatomyositis (DM) and polymyositis (PM) (Antiga et al., 2010) are associated with an increased cancer risk, though malignancy occurs more frequently and leads to increased mortality in DM (mortality ratio 3.8, 95%CI 2.9-4.8) (Sigurgeirsson et al., 1992; Buchbinder et al., 2001; Hill et al., 2001; Kuo et al., 2011). The RR of overall cancer in PM is only slightly elevated and comparable in both sexes (Males: RR 1.8, 95%CI 1.1-2.7; Female: RR 1.7, 95%CI 1.0-2.5). On the contrary the RR is considerably higher in DM (Males: RR 2.4, 95%CI 1.6-3.6; Female: RR 3.4, 95%CI 2.4-4.7) (Sigurgeirsson et al., 1992). Furthermore, the RR for malignancy in DM

compared to PM is 2.4 (95%CI 1.3-4.2) (Buchbinder et al., 2001). Reported SIR ranged from 3.0-6.2 for DM and from 1.3-2.0 for PM (Buchbinder et al., 2001; Hill et al., 2001; Kuo et al., 2011). The most common PM-associated neoplasias are represented by trachea/lung cancer and NHL (Sigurgeirsson et al., 1992; Hill et al., 2001) while stomach, colorectal, pancreas, prostate, breast, and ovarian cancers, in addition to trachea/lung cancer and NHL, are the most frequent malignancies in DM (Sigurgeirsson et al., 1992; Hill et al., 2001; Antiochos et al., 2009; Limaye et al., 2012). The risk for ovarian cancers is more noteworthy than others and the reported SIR is 10.5 (95%CI 6.1-18.1). More recently, Limaye et al. (2012) found no increased risk of malignancy in PM and the male sex and the older age at the diagnosis seem to be the more significant risk factors for cancer (Sigurgeirsson et al., 1992; Wakata et al., 2002; Chinoy et al., 2007; Antiochos et al., 2009; Kuo et al., 2011; Limaye et al., 2012). Fardet et al. (2009) identified other risk factors, represented by a rapid onset of symptoms (HR 3.11, 95%CI 1.07-9.02), the presence of skin necrosis (HR 3.84, 95%CI 1.00-14.85) or periungual erythema (HR 3.93, 95%CI 1.16-13.24), and a C4 low level (HR 2.74, 95%CI 1.11-6.75). Patients without routinely detected myositis-specific autoantibodies (anti-Jo-1, anti-PM-Scl, anti-U1-RNP, anti-U3-RNP, anti-Ku antibodies) have a higher risk of cancer associated myositis and negativity of the common autoantibodies panel is extremely sensitive (Chinoy et al., 2007). The autoantibody anti-p155 recently gained interest in defining the risk of cancer associated myositis and it has been detected only in DM and is strongly associated to cancer associated myositis (OR 23, 95%CI, 5.23-101.2) (Trallero-Araguas et al., 2012). The reported sensitivity is 78% (95%CI 45-94%), and specificity 89% (95%CI 82-93%). The positive predictive value is 58% and the negative predictive value 95% (Trallero-Araguas et al., 2012). Several studies reported that cancer may onset before, simultaneously or after the diagnosis of myositis, and the risk of cancer is considerably higher during the first years after diagnosis (Sigurgeirsson et al., 1992; Zantos et al., 1994; Hill et al., 2001; Antiochos et al., 2009; Kuo et al., 2011; Limaye et al., 2012). After 5 years the risk drops to the baseline in PM, however it remains elevated in DM (Hill et al., 2001). The occurrence before or within a year from the diagnosis strongly implies that inflammatory myositis is often paraneoplastic but the underlying pathogenetic mechanisms remain enigmatic. Casciola-Rosen et al. (2005) focused on common autoantigens coexpressed by neoplastic cells and regenerating myoblasts, suggesting that the immune response against tumor cells cross-reacts with undifferentiated muscle cells in cancer associated myositis. Histological signs of myositis were identified in colon cancer affected patients without clinical myopathy, evoking that peculiar tumoral factors play a major role in cancer associated myositis (Zampieri et al., 2010a; 2010b).

Polymyalgia rheumatica

The debate on the association between polymyalgia rheumatica and cancer is still open. Several case reports described this relationship (Keith and Gilliland, 2006;

Kafantari et al., 2008; Kountourakis et al., 2008), but only few studies were conducted in order to evaluate the risk with conflicting results. Myklebust et al. (2002) in a population study on about 400 patients, did not find an increased risk for neoplastic diseases in polymyalgia rheumatica. Similarly, in a case-control study including 42,676 lymphoma affected patients and 78487 controls, Askling et al. (2005b) did not detect a significant association between polymyalgia rheumatica and lymphoma. On the contrary, histological findings of temporal arteritis appeared to be related to an increased risk of cancer. In the same study, Haga et al. (1993) observed that the long interval between diagnosis of PMR and cancer (mean 6.5 years) did not support the case for a paraneoplastic syndrome. The most relevant longitudinal cohort study was conducted on nearly 40,000 patients during a period of 35 years. The reported SIR for overall cancers was 1.19 (95%CI 1.15-1.23), 2.26 (95%CI 2.10-2.42) within the first year from diagnosis. The most common cancers were stomach, lung, prostate, kidney, skin, acute myeloid leukemia, NHL and myeloma (Jiangang and Hemmink, 2010). Although results on cancer risk in polymyalgia rheumatica are still unclear and contrasting, malignancy screening is mandatory in patients presenting with polymyalgia rheumatica-like syndrome, characterized by age less than 50, asymmetrical involvement of typical sites, only one typical site involved, additional painful joints, and no response to steroid treatment (Naschitz et al., 1996).

The Role of Immunosuppressive Treatments

Prolonged immunosuppressive treatments may predispose to cancer development but proving a direct causative effect is challenging, as in the case of other adverse events. One confounding issue is represented by the fact that immunosuppressive treatment is restricted to patients with more aggressive diseases, which have already a higher cancer risk due to the disease activity. Moreover, several studies indicated that the increased risk of lymphoma in rheumatological patients is higher in the first years of the disease (Bjornadal et al., 2002; Bernatsky et al., 2005; 2009), suggesting that cumulative exposure to immunosuppressive drugs may have a relatively minor role. Despite these preliminary remarks, the available studies on the carcinogenicity of immunosuppressants in rheumatological diseases reported conflicting results. Asten et al. found that cancer incidence and cumulative drug exposure manifest a direct proportional relationship with an incidence rate ratio of 3.74 (95%CI 1.48-9.47) for the highest cumulative exposure group compared to the lowest (Asten et al., 1999). On the other hand, a meta-analysis confuted the hypothesis that non-steroidal anti-inflammatory drugs and corticosteroids contribute to the risk of lymphoma (Bernatsky et al., 2007) and a cohort study on 74651 RA patients reported that the use of steroids was associated to a lower risk of lymphoma (Hellgren et al., 2010). In a meta-analysis on the use of azathioprine (AZA) and 6-mercaptopurine, Kandiel et al. (2005) reported a RR of 4.18 (95%CI 2.07-7.51) for lymphoma development in IBD patients despite a very low

absolute risk. The higher risk of lymphoma development was confirmed in a large case-control study on 15,471 IBD cases (OR 3.22, 95%CI 1.01-10.81); on the contrary, the same study failed to demonstrate an increased risk of overall cancer in the treated group (OR 0.95, 95%CI 0.79-1.06) (Armstrong et al., 2010). In a different cohort study including over 19,000 patients with IBD, Beaugerie et al. found that the risk declined to the baseline following the withdrawal of azathioprine (Beaugerie et al., 2009). Further, there is additional concern about the risk of hepatosplenic T-cell lymphoma (HSTCL) in IBD-affected young men treated with azathioprine and infliximab (Mackey et al., 2007). However a meta-analysis showed that the risk for patients undergoing both treatments at once is comparable to that of the use of azathioprine only (Siegel et al., 2009).

Several studies addressed the lymphoma risk in patients treated with methotrexate (MTX) but the increased relative risk was comparable to the general population and not to non-exposed rheumatological patients (Salliot and van der Heijde, 2009). Further, some reports suggested that malignant lymphoma developed during MTX treatment spontaneously regresses after MTX withdrawal (Salloum et al., 1996) thus ultimately making this association one of the most controversial.

On the other hand, cyclophosphamide (CY) is a well known bladder carcinogen and its effect is dose-dependent; indeed, Travis et al. calculated a RR of 4.5 (95%CI 1.5-13.6) for bladder cancer, which increased to 6 and to 14.5 in patients respectively treated with 20-49 g and 50 g or more (Travis et al., 1995). The risk of bladder cancer has been assessed in SLE and was increased of about 25% from the predictable rate (SIR 1.23, 95%CI 0.66-2.11) (Bernatsky et al., 2008). For this reason, it is always prudent to prevent the risk, by adequate hydration, administration of 2-mercaptoethane sodium sulfonate (MESNA), and periodic screening for bladder cancer (urinary cytology and if necessary cystoscopy). An elevated risk of hematological malignancies, in particular acute myelogenous leukemia and myelodysplastic syndrome, has been also reported after CY-doxorubicin therapy for breast cancer and it is related to the high doses, 2400 mg/m² q 21 days x 2 or 4 cycles (Smith et al., 2003), possibly linked to the drug association and the high cumulative doses, rarely reached in rheumatological diseases. Lofstrom et al. could not reproduce the increased

risk of lymphoma development in SLE cases treated with CY (RR 1.1, 95%CI 0.3-3.3) (Lofstrom et al., 2007). On the contrary, Bernatsky et al. suggested an increased risk of hematological cancer in immunosuppressive treated patients (HR 2.29, 95%CI 1.02-5.15), including MTX, AZA and CY (Bernatsky et al., 2008). The 3-year incidence of cervical intraepithelial neoplasia (CIN) is reported to be higher in SLE (15%) than in the general population (9.8%) (Oggenovski et al., 2004), possibly secondary to the altered immune response to HPV in SLE affected women (Tam et al., 2004). Yearly pap-test is therefore advisable in SLE patients, particularly those treated with CY (Bernatsky et al., 2009).

The possible role biologics in carcinogenesis has generated much interest. A recent meta-analysis, on 63 RCTs of at least 6 months duration, assesses the cancer risk in RA affected patients treated with biologics, in particular adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, and tocilizumab. No statistically significant increased risk of cancer was detected in biologics group compared with other DMARDs or placebo (Lopez-Olivo et al., 2012). However, in a recent prospective study performed in Denmark between 2000 and 2008, Dreyer et al. reported an equal risk of lymphoma and overall cancer, but a higher risk in colon malignancies in TNF exposed compare to non exposed population (HR 3.52) (Dreyer et al., 2012). A slightly higher, but not statistically significant, cancer risk was found in a meta-analysis on randomized clinical trials conducted on RA treated with anti-TNF α biologics (Wong et al., 2011). These data were confirmed in the meta-analysis conducted by Mariette et al. (2011), which showed that anti-TNF did not increase the risk of overall cancer, lymphoma in particular. Nevertheless they found a significant higher risk of skin cancer (Mariette et al., 2003). The same higher risk of skin cancer was established in a large US observational study (Wolfe and Michaud, 2007). The risk of lymphoma did not increase in the case-control study of Askling et al. (Askling et al., 2009). Prior reports on the risk of anti-TNF α were controversial and numerous single studies failed to demonstrate a greater risk of cancer (Askling et al., 2005a; 2005b; Setoguchi et al., 2006). A meta-analysis on 9 RCTs showed an evidence of a dose-dependent increased risk of cancer in infliximab and adalimumab exposed RA patients. However, malignancies did not accumulate in time of exposure, suggesting that

Table 3. Established and Proposed Associations between Immunosuppressive Drugs and Cancer

Drug	Cancer	References
AZA	Lymphoma	(Kandiel et al., 2005; Armstrong et al., 2010)
	HSTCL	(Mackey et al., 2007; Siegel et al., 2009)
MTX	Lymphoma	(Salloum et al., 1996; Wolfe and Michaud, 2004; Salliot and van der Heijde, 2009)
CY	Bladder	(Bernatsky et al., 2008)
	Cervix	(Oggenovski et al., 2004)
	Lymphoma	(Lofstrom et al., 2007; Bernatsky et al., 2008)
Anti-TNF α	Lymphoma	(Wolfe and Michaud, 2004; Askling et al., 2005a; Askling et al., 2005b; Bongartz et al., 2006; Setoguchi et al., 2006; Askling et al., 2009; Mariette et al., 2011; Raaschou et al., 2011; Wong et al., 2011; Lopez-Olivo et al., 2012)
	HSTCL	(Kotlyar et al., 2011; Parakkal et al., 2011)
	Skin	(Wolfe and Michaud, 2007; Mariette et al., 2011)
	Colon	(Dreyer et al., 2012)

anti-TNF α accelerate the clinical onset of pre-existing neoplasia, rather than inducing a new one (Bongartz et al., 2006). Similarly, Wolfe et al. (2007) found a slightly greater risk of lymphomas in anti-TNF treatment. The SIR for patients receiving anti-TNF was 2.9 (95%CI 1.7-4.9) and that for patients not taking MTX nor biologics was 1.0 (95%CI 0.4-2.5). The authors argued that the higher risk in the exposed group could be related to the more active and aggressive rheumatological diseases, that required anti-TNF treatment (Wolfe and Michaud, 2007). Finally, cancer stage at diagnosis and outcome do not differ significantly in anti-TNF exposed compared with non biologics-exposed RA patients (Raaschou et al., 2011). As previously mentioned, the co-treatment with anti-TNF α and AZA carries an increased risk of HSTCL in young male IBD affected patients (Kotlyar et al., 2011). However, Parakkal et al. (2011) found that HSTCL can also occur in patients with RA, female and older patients treated with anti-TNF α and immunomodulator (thiopurines or MTX).

Conclusions

Cancer and autoimmunity share common pathogenetic pathways with immune dysregulation representing the baseline mechanism of both conditions and confers reciprocal susceptibility. Patients with autoimmune diseases have a higher risk of cancer, which is established by several factors, from intrinsic immunological characteristics to individuals and environmental factors, to drug effect. From a clinical point of view, it is crucial to be aware of the cancer risk, including not only hematological malignancies, but also solid cancer, like CIN in SLE, or bladder cancer in CY treated patients, in order to make an adequate prevention. Furthermore, the clinician should identify features that predispose to cancer, like inflammatory activity in RA, and at the same time recognize those clinical and serological markers that have a predictive role in some autoimmune diseases. The greater consciousness of risk factors and predictive issues allow to recognise the first signs and symptoms of cancer development and, as a result, to diagnose it earlier. From a pathogenetic standpoint we submit that animal models, epidemiology, and toxicology should provide a collaborative effort to provide answers to the numerous open issues.

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