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Antinuclear antibodies and cancer: A literature review

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ABSTRACT

Antinuclear antibodies (ANAs) are a spectrum of autoantibodies targeted to various nuclear and cytoplasmic components of the cells. They are very useful as serological markers for different autoimmune disease, like systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), scleroderma, polymyositis, or mixed connective tissue disease. In these years, an increasing attention has been focussed in the relationship between tumours and autoimmunity. Different authors have demonstrated that ANAs are presented, not only in autoimmune diseases, also in serum of patients with different types of cancers. These data suggested that ANAs could be involved in the pathogenesis of cancer as well as other premalignant disease. In this review, we are going to describe all data reported about the presence of these antibodies in samples from patients with cancer as well as the potential role of some of these proteins in early detection and prognosis.

1. Introduction

Antinuclear antibodies (ANAs) are a spectrum of autoantibodies that react with various nuclear and cytoplasmic components of normal human cells. The development of autoantibodies is the consequence of breakdown of immunologic tolerance, but their presence is not exclusive of autoimmune conditions. They are very important serological markers for different autoimmune disease, like connective tissue diseases (CTD)—eg, systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), scleroderma (SSc), polymyositis (PM), or mixed connective tissue disease (MCTD). In these years, an increasing attention was focussed in the relationship between tumours and autoimmunity. In cancer setting, autoantibodies have been classically considered to be epiphenomena probably related to the release of tumor neoantigens proteins, although the interpretation of positive serologic findings in this setting remains controversial,

Several authors have suggested that ANAs, are not only related to autoimmune diseases, also to different types of cancers. These data suggested that ANAs could be associated to the pathological processes of cancers and other premalignant disease (Zou et al., 2015; Imran et al., 2003). Some authors have demonstrated that autoantibodies in cancer sera many appear many years before the diagnosis of cancer (Fernandez-Madrid et al., 1999), suggesting that the process leading to autoantibody formation in patients with cancer occurs during the early stages of tumorigenesis.

ANAs detection is made by an immunofluorescent imaging technique, using tissue culture cells such as HEp2, derived from a patient with cervix carcinoma, as the substrate for reaction with autoimmune sera. The results of ANA testing are reported in two parts: the titre of the antibodies and the staining pattern produced by these antibodies (the distribution of staining produced by autoantibodies reacting with antigens in the nucleus and cytoplasm). Therefore, many types of ANAs and different classifications have been described according to the staining pattern (nuclear, cell-cycling and cytoplasmic), the antigens against are targeted (nucleasomes and DNA-associated proteins; RNA-associated proteins; ribosomes and nucleoli; membranes and nuclear matrix) or the autoimmune process (SLE; SS, MTCD; SSc; vasculitis, reumathoid arthritis (RA) (Cabrera et al., 2016).

Recently an international workshop arrived at a consensus on the nomenclature of ANA staining patterns and gradually a more appropriate name for ANA will be used: anti-cellular antibodies (AC) (Chan et al., 2015; Kavanaugh and Solomon, 2002). This workshop describes three broad categories of ANA staining patterns: nuclear, cell cycle-associated (mitotic), and cytoplasmic. These categories comprise 29 individual staining patterns coded AC1-29. It is to be expected that the number of coded patterns will increase, as more staining patterns are well established. Each individual staining pattern is produced by one or several specific autoantibodies (Table 1).

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Table 1
Antigens recognized by ANA antibodies.

Antigens	Antibodies
Nucleosomes and DNA associated proteins	Anti-DNA native y monocatenary Antihistones (H1-H4) Anti-DNA topoisomerase I (Scl-70) y II Anticentromere A, B y C Anti-PCNA/cicline Anti-HMG, LMG, Ku, Ki y SL
RNA-associated proteins	Anti-Ro/SSA (60 y 52 kD) Anti-La/SSB Anti-U1-RNP (A y C) y U2-RNP (A" y B") Anti-Sm BB" y D Anti-aminoacil-sintetases t-RNA (Jo-1, etc…)
Nucleoli and ribosomes	Anti-RNA polimerase I, II y III Anti-PM/Scl Ribosomal Antiprotein (P0, P1 y P2) Anti-NOR 90 Anti-U3-RNP/fibrilarine Anti-B 23/nucleoplasmine Anti-C 23, Th/to, SRP y MAS Anti-RNA y ribonuclease P
Membranes and nuclear matrix:	Anti-lamines A, B y C Nuclear antipores Antirreceptor lamine B Anti-A1 y A2 hn RNP
Other ANAs	Anti-Mi1 y Mi2 Anti-Su, Me, Ma y HaT1

A huge amount of classical research studies and meta-analysis on ANAs, have demonstrated that they are associated to several rheumatic autoimmune disorders. Different ANAs have been described and it became clear that some ANAs were highly specific and associated predominantly with one disease, such as autoantibodies to double-strand DNA and to Sm antigen in SLE, anti-DNA topoisomerase 1 and anticentromere in scleroderma and the CREST syndrome, and anti-transfer RNA-synthetases in dermato/polymyositis. Other ANAs such as antihistones are present in several diseases, including SLE and rheumatoid arthritis (Kavanaugh and Solomon, 2002). Nevertheless, combinations of ANAs with high specificity and others with lower specificity produced different ANA profiles that were useful in differential diagnosis of clinical disorders. However, not only autoimmune diseases are associated to this type of makers and there is an increasing interest about the role of these proteins in carcinogenesis (Mohammed and Abdelhafiz, 2015; Rehman, 2015; Tan, 2014).

In recent years, the development of immunotherapy in cancer, has generated a growing enthusiasm for the search for immunological markers able to predict the response to these types of treatments, as well as searching a potential toxicity. Various biomarkers such as of PDL1 expression in tumor cells and infiltrating lymphocytes as well as tumor mutational burden (TMB), are the most known factors and with a certain correlation with the degree of response, especially anti-PD1 or antiPDL1-1. On the role that ANAs can play in predicting the response as well as in the prognosis of patients treated with immunotherapy, there are very few existing data refer more to preclinical studies than to clinical experience. In relation to the toxicity of these antibodies, it is widely known that one of the most dependent side effects of class is autoimmune toxicity. The presence of thyroid, hepatic, intestinal, pulmonary and even central disorders, as for example hypophysitis, have been described in all studies evaluating the role of immunotherapy in different tumors. These alterations are based on basic autoimmune disorders and when they appear, it is not uncommon for them to associate the presence of antinuclear antibodies, as would occur in sporadic cases. Therefore, the presence of ANAs in cancer patients is not rare, especially if the context of pharmacological autoimmune complications is present (Läubli et al., 2017a; Zen and Yeh, 2018).

However, in spite of the lack of information about ANAs and immune-cancer therapy, in this review we will try to describe all published data about the potential relationship between ANAs and this new cancer approach as well as the role of these proteins in specific toxicity.

2. ANAs and tumors

As previously was described, ANAs are usually found in systemic rheumatic diseases. It is no rare to find these proteins also in various cancer sera patients (Burnham, 1972).

In this study, we are going to review how these well-known ANAs involved in the diagnosis of some autoimmune diseases (ADs) such as systemic lupus erythematosus (SLE), scleroderma, and dermatomyositis (DM)/polymyositis (PM) could also be potential diagnostic and prognostic biomarkers for cancer (Tan, 1989).

However, ANAs in cancer sera were for a long time regarded as epiphenomena without a clear clinical relevance and the interpretation of the role of these autoantibodies in cancer sera remained controversial. Although there are examples of autoantibodies commonly found in autoinmune diseases such as anti-DNA, anti-Sm, anti-RNP, and other antibodies, a large number of the autoantibodies are also found in cancer sera without autoantigens classically associated with the autoinmune diseases (Sahin et al., 1995).

As previously was mentioned, antinuclear antibody (ANAs) testing is useful for screening, diagnosis and follow-up of patients with systemic rheumatic diseases. Indirect immunofluorescence (IIF) on HEp-2 cells is the gold standard for ANA testing.

However, ANAs have also been detected in patients with different cancer types with or without any autoimmune disease (Table 2). To

Table 2
Correlation between autoinmune disease, ANAS and tumors with positive titre.

Colagenosis	ANAs	Tumors related with positive titre
SLE	Anti-DNA native y monocatenary	Tymoma, lymphoma Maire et al. (2013), Erkanli et al. (2006), lung cancer Riska et al. (1978), MALT and NHL Erkanli et al. (2006)
	Antihistones	
	Anti-Sm	Lung, pancreatic, colon and cervical cancer Lü et al. (2005)
	Anti-Ro/SSA	Lymphoma, myeloma Sakamoto et al., 1992), teratocarcinoma Ochs et al. (2016)
	Anti-La/SSB	NHL Huang et al. (2007), squamous cell carcinoma Bhargavan et al., (2012)
	Antiproteíns P ribosomals, Antifosfolípides	NHL Higuchi et al. (2000)
	Anti-PCNA.	Lymphoma Gantzer et al. (2011), Miyagawa et al. (1996)
Esclerodermia	Anticentromere, anti-DNA	Breast and lung cancer Rattner et al. (1997)
	Topoisomerase I (Scl-70),	Lung cancer Läubli et al. (2017b), Lerner et al. (1981), ovarian and breast cancer Läubli et al. (2017b)
	Antinucleolar (PM/Scl, RNA polimerase, etc.)	Breast, lung and haematological cancer Kyndt et al., (1997)
Sjögren Syndrome	Anti-Ro/SSA	NHL Huang et al. (2007), squamous cell carcinoma Bhargavan et al. (2012)
	Anti-La/SSB	NHL Higuchi et al. (2000)
Polimiositis	Antiaminoacil-sintetases t-RNA (Jo-1, etc.)	Lung cancer, NHL and renal cell cancer Keesee et al. (1996)
	Anti-Mi	
	Anti-PM/Scl	