Table 6-10 Autoantibodies in Systemic Autoimmune Diseases

Disease	Specificity of Autoantibody	% Positive	Association with Specific Disease Features
Systemic lupus erythematosus (SLE)	Double-stranded DNA	40-60	Nephritis; specific for SLE
	U1-RNP	30-40	
	Smith (Sm) antigen (core protein of small RNP particles)	20-30	Specific for SLE
	Ro (SS-A)/La (SS-B) nucleoproteins	30-50	Congenital heart block; neonatal lupus
	Phospholipid-protein complexes (anti-PL)	30-40	Antiphospholipid syndrome (in ~10% of SLE patients)
	Multiple nuclear antigens ("generic ANAs")	95-100	Found in other autoimmune diseases, not specific.
Systemic sclerosis	DNA topoisomerase 1	30-70	Diffuse skin disease, lung disease; specific for systemic sclerosis
	Centromeric proteins (CENPs) A, B, C	20-40	Limited skin disease, ischemic digital loss, pulmonary hypertension
	RNA polymerase III	15-20	Acute onset, scleroderma renal crisis, cancer
Sjögren syndrome	Ro/SS-A La/SS-B	70-95	
Autoimmune myositis	Histidyl aminoacyl-tRNA synthetase, Jo1	25	Interstitial lung disease, Raynaud phenomenon
	Mi-2 nuclear antigen	5-10	Dermatomyositis, skin rash
	MDA5 (cytoplasmic receptor for viral RNA)	20-35 (Japanese)	Vascular skin lesions, interstitial lung disease
	TIF1γ nuclear protein	15-20	Dermatomyositis, cancer
Rheumatoid arthritis	CCP (cyclic citrullinated peptides); various citrullinated proteins	60-80	Specific for rheumatoid arthritis
	Rheumatoid factor (not specific)	60-70	

Listed autoantibodies are associated with high frequencies with particular diseases. "Generic" antinuclear antibodies (ANAs), which may react against many nuclear antigens, are positive in a large fraction of patients with SLE but are also positive in other autoimmune diseases. % positive refers to the approximate % of patients who test positive for each antibody.
The table was compiled with the help of Dr. Antony Rosen, Johns Hopkins University.

- *Homogeneous or diffuse nuclear staining* usually reflects antibodies to chromatin, histones, and, occasionally, double-stranded DNA.
- *Rim or peripheral staining* patterns are most often indicative of antibodies to double-stranded DNA and sometimes to nuclear envelope proteins.
- *Speckled pattern* refers to the presence of uniform or variable-sized speckles. This is one of the most commonly observed patterns of fluorescence and therefore the least specific. It reflects the presence of antibodies to non-DNA nuclear constituents such as Sm antigen, ribonucleoprotein, and SS-A and SS-B reactive antigens.
- *Nucleolar pattern* refers to the presence of a few discrete spots of fluorescence within the nucleus and represents antibodies to RNA. This pattern is reported most often in patients with systemic sclerosis.
- *Centromeric pattern.* Patients with systemic sclerosis often contain antibodies specific for centromeres, which give rise to this pattern.

The fluorescence patterns are not absolutely specific for the type of antibody, and because many autoantibodies may be present, combinations of patterns are frequent. Concerns have been raised about the sensitivity and subjective nature of this assay, and attempts are ongoing to replace it with ELISA for specific nuclear and other antigens. Nevertheless, the staining pattern is considered of diagnostic value, and the test remains in use. **Antibodies to double-stranded DNA and the so-called Smith (Sm) antigen are virtually diagnostic of SLE.**

Other Autoantibodies. In addition to ANAs, lupus patients have a host of other autoantibodies. Some are directed against blood cells, such as red cells, platelets, and lymphocytes; others react with proteins in complex with phospholipids. *Antiphospholipid antibodies* are present in 30% to 40% of lupus patients. They are actually directed against epitopes of plasma proteins that are revealed when the proteins are in complex with phospholipids. Included among these proteins are prothrombin, annexin V, β_2-glycoprotein I, protein S, and protein C. Antibodies against the phospholipid-β_2-glycoprotein complex also bind to cardiolipin antigen, used in syphilis serology, and therefore lupus patients may have a false-positive test result for syphilis. Some of these antibodies interfere with in vitro clotting tests, such as partial thromboplastin time. Therefore, these antibodies are sometimes referred to as *lupus anticoagulant*. Despite the observed clotting delays in vitro, however, patients with antiphospholipid antibodies have complications related to excessive clotting (a *hypercoagulable state*), such as thrombosis (Chapter 4).

Etiology and Pathogenesis of SLE

The fundamental defect in SLE is a failure of the mechanisms that maintain self-tolerance. Although what causes this failure of self-tolerance remains unknown, as is true of most autoimmune diseases, both genetic and environmental factors play a role.

Genetic Factors. SLE is a genetically complex disease with contributions from MHC and multiple non-MHC genes. Many lines of evidence support a genetic predisposition.

- Family members of patients have an increased risk of developing SLE. As many as 20% of clinically unaffected first-degree relatives of SLE patients reveal autoantibodies and other immunoregulatory abnormalities.
- There is a higher rate of concordance (>20%) in monozygotic twins when compared with dizygotic twins (1% to 3%).
- Studies of HLA associations support the concept that MHC genes regulate production of particular