

characteristic of Treg cells, or, more likely, activation of effector T cells. Similarly, although termed T_H1 cells, the origins of these cells remain obscure, including whether they represent a unique developmental pathway or, more likely, a differentiation pathway of preexisting T helper lymphocytes. However, what is consistent is that each of these studies has found cells capable of making high levels of IL-10 ($\pm$ TGF- β) consistent with the T_H1 cell type, and current concepts focus on the integral role of these IL-10-producing cells in immune tolerance to allergens in healthy subjects and after immunotherapy.

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4. Autoimmunity, vasculitis, and autoantibodies

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Autoimmune diseases are distinct clinical syndromes characterized by various alterations in normal immune responsiveness, such that there is a loss of tolerance to particular host constituents. In most cases, despite years of intense investigation, the etiopathogenic antigens initiating these systemic inflammatory conditions remain undefined. However, a great deal has been learned about the changes in components of the immune response relevant to the propagation and sustenance of these often chronic disorders. In addition, various hormonal, environmental, physiologic, and other influences that affect their expression have been identified. The expression and ultimate clinical outcome of autoimmune diseases usually relate to inflammation-related damage to the target organ with subsequent dysfunction. Certain immune conditions, such as autoimmune thyroid disease, largely affect a single organ, whereas others, such as systemic lupus erythematosus, heterogeneously affect sundry organ systems. Autoantibodies directed against normal host

antigens are a common feature of many autoimmune diseases. In some cases they are pathogenic, whereas in others they serve as markers for organ involvement or outcomes. Clinical descriptions of autoimmune diseases date back many decades in some cases. Recent efforts at formulating classification criteria have allowed clearer distinctions and more accurate stratification. Greater understanding of the immunopathogenesis of autoimmune conditions has led to the development and introduction into the clinic of novel immunomodulatory therapies and treatment paradigms that have substantially improved the outcomes for patients affected by these serious conditions. (*J Allergy Clin Immunol* 2006;117:S445-50.)

Key words: Rheumatoid arthritis, systemic lupus erythematosus, vasculitis, autoantibodies

Autoimmune diseases are characterized by dysregulation in various components of immune response. Traditionally, they have been categorized as either cell mediated, with a particular role for T_H1 T cells, or humoral, with autoantibodies playing a key role in certain disease manifestations. In addition, it is now understood that components of the inflammatory responses (eg, cytokines) might be relevant and common to tissue damage in diverse autoimmune conditions. With a greater understanding of pathogenesis coupled with the advances in

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Abbreviations used

ACR:	American College of Rheumatology
C-ANCA:	Cytoplasmic staining antineutrophil cytoplasmic antibody
CCP:	Cyclic citrullinated peptide
CSS:	Churg-Strauss syndrome
dsDNA:	Double-stranded DNA
GCA:	Giant cell arteritis
GN:	Glomerulonephritis
HCQ:	Hydroxychloroquine
IC:	Immune complex
LCV:	Leukocytoclastic vasculitis
MPA:	Microscopic polyangiitis
NSAID:	Nonsteroidal anti-inflammatory drug
RA:	Rheumatoid arthritis
RF:	Rheumatoid factor
RNP:	Ribonucleoprotein
SLE:	Systemic lupus erythematosus
WG:	Wegener's granulomatosis

pharmaceutical development, biologic agents directed at specific components of the immune system have become available for the treatment of various autoimmune diseases. As a means to review the pathogenesis, therapy, and potential roles of various autoantibodies in the development of autoimmune diseases, this article will focus on 2 of the most prevalent autoimmune diseases (rheumatoid arthritis [RA] and systemic lupus erythematosus [SLE]) cared for by rheumatologists-immunologists. In addition, the latest classification criteria for vasculitis, a group of diseases relevant for rheumatologists and allergists-immunologists, will be reviewed.

RHEUMATOID ARTHRITIS

Background

RA is a chronic systemic inflammatory condition of unknown cause that affects approximately 0.8% of the population worldwide. Women are affected 3 times as often as men, and the peak incidence occurs between 40 and 60 years, but all ages can be affected.

Pathogenesis

A strong association between the expression of certain class II MHC subtypes (HLA-DRB1*0101, *0102, *1001, *0401, *0404, *0405, and *0408) and the development and severity of RA has been well documented. These HLA-DR molecules contain the shared epitope, a sequence of amino acids in the third hypervariable region of the β chain, which confer susceptibility to RA.

RA is characterized by synovitis within diarthrodial joints. Angiogenesis is an important early event. Among the numerous cell types present within the inflamed joint, CD4 helper T cells with a T_H1 phenotype appear to play a key role in orchestrating the immune response. Activation of T cells requires cognate interaction of antigen/T-cell receptor/MHC molecules in conjunction with a second

signal that is provided by various costimulatory molecules. Activation occurs more efficiently in an inflammatory milieu, suggesting interplay between the innate and specific immune systems. Activated macrophages are an important source of inflammatory factors, including key proinflammatory cytokines, such as TNF- α and IL-1. Among their many activities, TNF and IL-1 promote accumulation of inflammatory cells and the synthesis of other cytokines, chemokines, matrix metalloproteinases, and other inflammatory mediators. B cells contribute to the ongoing inflammation by activating T cells and producing potentially pathogenic autoantibodies: rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP).

Diagnosis

The presence of 4 or more of the following American College of Rheumatology (ACR) criteria for more than 6 weeks has a 92% sensitivity and 89% specificity for RA: stiffness of the joint lasting greater than 1 hour; arthritis of 3 or more joints; arthritis of proximal interphalangeal, metacarpophalangeal, or wrist joints; symmetric arthritis; rheumatoid nodules; seropositivity for RF; and radiographic erosions, periarticular osteopenia, or both. In addition to characteristic articular involvement, RA is associated with several extra-articular manifestations, including dermatologic (eg, rheumatoid nodules and vasculitis), pulmonary (eg, pleuritis and interstitial pneumonitis), ocular (eg, scleritis and Sjögren's syndrome), hematologic (eg, Felty's syndrome), and renal (eg, amyloidosis and interstitial nephritis).

Serum RF, which is found in 80% or more of the sera of patient with RA, is associated with poorer prognosis. However, whether this autoantibody plays a pathogenic role in the development of the disease or its progression remains unknown. RF is not specific for RA because it is seen in 5% of the general population and might be found in up to 20% of healthy elderly persons. It is also present in other diseases, such as Sjögren's syndrome, cryoglobulinemia, lupus, bacterial endocarditis, viral hepatitis, and malignancy. Anti-CCP is directed against citrullinated peptide residues present within inflammatory sites. Although the citrullination occurs in many conditions, the development of an immune response against CCP appears to be relatively specific for RA. Similar to RF, the pathogenic role of anti-CCP remains unknown. However, it has a greater specificity for RA than RF and might precede the development of arthritis.¹⁻⁵

Treatment

The primary goals of therapy for RA are relief of pain, reduction of inflammation, preservation of functional status, prevention of disease and therapy complications, and resolution of the pathogenic process. Historically, RA had been viewed as a benign disease, and it was managed conservatively, starting with nonsteroidal anti-inflammatory drugs (NSAIDs). However, it is now established that RA is an aggressive disease associated with substantial morbidity and accelerated mortality. Subsequently, the treatment has become more aggressive,

TABLE I. Specificities of antinuclear antibodies⁶

(PRIVATE) Specificity	Antigen recognized	Frequency in SLE	Frequency in other diseases	Clinical associations
DNA	dsDNA	50%-60% (might vary with disease activity)	Very uncommon	Lupus nephritis, severe active disease
Smith	U1, U2, U4-6 snRNP	30%-40%	Very uncommon	Interstitial lung disease
Ribonucleoprotein	U1 snRNP	30%-40%	>90% of patients with MCTD	MCTD symptoms overlap SLE, DM/PM, PSS
Ro (SS-A)	60 kd of RNA-binding protein	25%-30%	60% Sjögren's syndrome	Subacute cutaneous lupus, neonatal lupus
La (SS-B)	50-kd RNA-binding protein	10%-15%	50% Sjögren's syndrome	
Histone	Histone proteins H1, H2A, H2B, H3, H4	50%-70%	95% drug-induced lupus	>30% idiopathic SLE
Scl-70	Topoisomerase I	<5%	40%-70% PSS	
Centromere	70/13-kd nuclear proteins	<5%	70%-85% CREST	Raynaud's phenomenon
Jo-1	Histidyl-tRNA synthetase	<5%	40%-50% DM/PM	Interstitial lung disease, arthritis

snRNP, Small nuclear ribonucleoprotein; *MCTD*, mixed connective tissue disease; *DM*, dermatomyositis; *PM*, polymyositis; *PSS*, progressive systemic sclerosis; *CREST*, calcinosis, Raynaud's syndrome, esophageal motility, sclerodactyly, telangiectasia; *tRNA*, transfer RNA.

with earlier institution of treatment with disease-modifying antirheumatic drugs and TNF- α inhibitors (etanercept, infliximab, and adalimumab). Commonly used disease-modifying antirheumatic drugs include methotrexate, hydroxychloroquine (HCQ), sulfasalazine, and leflunomide. With a better understanding of the immunopathogenesis of the disease, other immunomodulatory approaches are under investigation, including the use of cytotoxic T lymphocyte-associated antigen 4-Ig, anti-CD20 mAb, and inhibitors of signaling molecules, chemokines, and adhesion molecules.

SYSTEMIC LUPUS ERYTHEMATOSUS

Background

SLE, often considered the prototypical systemic autoimmune disease, typically affects women of childbearing age (15-40 years). SLE is characterized by the presence of multiple autoantibodies that react with various components of the cell nucleus. Specific autoantibodies might correlate with particular organ involvement and prognosis in SLE and in related autoimmune conditions (Table I).⁶ Unlike many autoantibodies, such as SS-A, SS-B, and anti-Smith, double-stranded DNA (dsDNA) has been shown to be pathogenic in SLE. A higher titer of dsDNA and its deposition along the glomeruli has been associated with active glomerulonephritis. Similarly, antiphospholipid antibodies have been associated with the hypercoagulable state in many autoimmune conditions, including SLE. *In vitro* data have demonstrated an activation of the clotting cascade by APL antibodies, but their exact pathogenic role has not been fully elucidated.

Pathogenesis

The striking female predominance (10:1) and results from animal data suggest that sex hormones play a key

role in the pathogenesis of SLE. Genetic associations have been observed with certain MHC alleles (HLA-B8, HLA-DR2, and HLA-DR3), null alleles for complement protein C4, and Fc γ receptor alleles. Recent work has suggested that a loss of immune tolerance to self-antigen through alternative splicing might introduce novel antigenic epitopes, increasing the risk for development of autoimmune diseases.⁷

Diagnosis

The presence of 4 or more of the following 11 ACR criteria yields a sensitivity and specificity of 95% in SLE: malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neuropsychiatric disorder, hematologic disorder, immunologic disorder (antiphospholipid antibody or anti-dsDNA or anti-Smith or false-positive result for syphilis), and antinuclear antibody. In addition, patients with SLE often present with constitutional symptoms, oral-nasal ulceration, Raynaud's phenomenon, and central and peripheral nervous system involvement among other symptoms.

Treatment

The therapy of SLE depends on the particular organ system involvement. Patients with arthritis respond well to NSAIDs and HCQ, whereas rashes might respond well to HCQ and topical steroids. Other minor manifestations can often be controlled with low-dose steroids (eg, 0.5 mg/kg/d prednisone), whereas moderate and severe manifestations, such as glomerulonephritis (GN) or cerebritis, might require higher doses and other immunosuppressants, such as cyclophosphamide, azathioprine, and mycophenolate mofetil. A great deal of research is currently ongoing to assess the efficacy of targeting B cells (eg, with anti-CD20 mAb and BLyS/BAFF inhibitors).

VASCULITIS

Vasculitis refers to the presence of inflammation within blood vessel walls, with subsequent vessel damage and end-organ ischemia. Although many attempts have been made to classify vasculitis (eg, according to types of inflammation, causative mechanism, and associated autoantibodies), the most commonly used classification system is based on the size of vessels predominantly involved and distinguishing clinical characteristics.

Small-vessel vasculitis

Leukocytoclastic vasculitis. Leukocytoclastic vasculitis (LCV) has been associated with the use of certain medications (eg, penicillin, diuretics, and phenytoin), infections (eg, hepatitis B/C and HIV), and malignancies; however, in many cases, no cause can be found. It is characterized by the immune complex (IC) deposition within affected vessels. The presence of 3 or more of the following ACR criteria yields a 71% sensitivity and 84% specificity for diagnosis: age greater than 16 years, palpable purpura, maculopapular rash, possible offending agents with temporal relationship, and biopsy showing neutrophils around arterioles and venules. Most cases resolve on withdrawal of the inciting agent or spontaneously. However, steroids might be required in refractory cases.

Henoch-Schönlein purpura. Henoch-Schönlein purpura presents similarly to LCV but occurs predominantly in children between the ages of 2 and 11 years, often after an upper respiratory tract infection. It is characterized by deposition of IgA containing IC within the vessel wall.⁸ The presence of 2 or more of the following ACR criteria provides an 87% sensitivity and specificity for diagnosis: age less than 20 years, palpable purpura, bowel angina, and wall granulocytes on biopsy characteristic of LCV. Patients might also present with arthralgia, hematuria, and/or proteinuria. Similar to LCV, more than 90% of cases resolve without specific intervention. However, steroids might be required in refractory cases.

Cryoglobulinemia. Cryoglobulins, Igs that precipitate in the cold (<37°C) and dissolve on rewarming, can be classified as follows: type I (monoclonal Ig), type II (mixed monoclonal immunoglobulin with RF activity and polyclonal Ig), and type III (mixed polyclonal Ig). Type I is associated with lymphoproliferative disorders, such as multiple myeloma and Waldenstrom's macroglobulinemia, and often presents with hyperviscosity, thrombosis, and purpura. Type II is associated with chronic viral infections, such as hepatitis C and HIV, whereas type III is associated with underlying autoimmune diseases. Patients with type II or III often present with palpable purpura, neuropathy, lymphadenopathy, and renal disease. The goal of the therapy is to treat the underlying condition, with concomitant immunomodulatory therapies in severe-refractory cases.

Microscopic polyangiitis. Microscopic polyangiitis (MPA) typically affects men in their fourth and fifth decades. Patients present with constitutional symptoms, necrotizing GN, alveolar hemorrhage, palpable purpura,

neuropathy, and gastrointestinal bleeding. Despite its association with perinuclear staining anti-neutrophil cytoplasmic antibody (with specificity for myeloperoxidase) in 60% of cases, MPA is characterized by few IC deposits at sites of necrotizing vasculitis. A smaller number of patients (40%) have cytoplasmic staining antineutrophil cytoplasmic antibody (C-ANCA) with reactivity against proteinase 3. Because of severe potential end-organ damage, patients are usually treated with a combination of steroids and cytotoxic agents, most commonly cyclophosphamide.

Hypocomplementemic urticarial vasculitis. Hypocomplementemic urticarial vasculitis usually affects women, with a peak incidence in the fourth decade. It shares multiple characteristics with SLE, such as hypocomplementemia, urticaria, venulitis on biopsy, arthralgia-arthritis, uveitis-episcleritis, GN, abdominal pain, lymphadenopathy, and low C1q. Unlike SLE, hypocomplementemic urticarial vasculitis has been associated with obstructive pulmonary disease.⁹ Treatment includes antihistamines, NSAIDs, colchicine, HCQ, and dapsone for skin manifestations. Steroids can be added in refractory cases.

Medium-vessel vasculitis

Wegener's granulomatosis. Similar to MPA, Wegener's granulomatosis (WG) occurs more commonly in men in their 40s. Unlike MPA, it affects both small and medium vessels and is associated with C-ANCA (50% to 90% with reactivity to proteinase 3). Despite its high specificity, the mechanisms of its production and any specific pathogenic role for C-ANCA in WG remain unknown. The presence of 2 or more of the following ACR criteria yields an 88% sensitivity and 92% specificity for diagnosis: nasal-oral inflammation, abnormal chest radiograph (nodules, cavities, or fixed infiltrates), hematuria, and/or granulomatous inflammation of an artery or perivascular area on biopsy. In addition, patients with WG can present with fever, pauci-immune GN, and neuropathy. Daily oral cyclophosphamide (1-2 mg/kg) in combination with steroids is the standard treatment. Relapses are common in patients with active but not life-threatening disease or those in disease remission. Azathioprine, mycophenolate mofetil, and methotrexate have been used as alternatives to cyclophosphamide to minimize toxicity. A recent multisite study evaluating the role of a TNF, etanercept, has failed to show its effectiveness in the treatment of WG. Of concern, side effects and solid cancers were more common in the TNF inhibitor-treated group.¹⁰

Polyarteritis nodosa. Polyarteritis nodosa is a pauci-immune necrotizing vasculitis of small and medium muscular arteries affecting predominantly middle-aged men. The presence of 3 or more of the following ACR criteria yields an 82% sensitivity and 87% specificity for diagnosis: weight loss of greater than 4 kg, livedo reticularis, testicular pain, polyneuropathy-myalgia, new onset of diastolic blood pressure of greater than 90 mm Hg, renal disease (blood urea nitrogen >40 mg/dL or creatinine >1.5 mg/dL), hepatitis B infection, angiogram with characteristic aneurysms, and leukocytes around small- or medium-sized arteries on biopsy. Treatment entails a

TABLE II. Other autoimmune diseases

Condition	Clinical findings	Autoantibody	Treatment
Antiphospholipid syndrome	Venous-arterial thrombosis, thrombocytopenia, spontaneous abortions	Anticardiolipin antibody, lupus anticoagulant, anti- β_2 -glycoprotein-I antibody	Anticoagulation (INR >2), aspirin plus heparin in pregnancy
Sjögren's syndrome	Xerophthalmia, xerostomia (sicca symptoms), arthritis, interstitial nephritis, renal tubular acidosis, pulmonary involvement	ANA, SS-A, SS-B, RF	Symptomatic (muscarinic agonists, cyclosporine ophthalmic drops, artificial tears), immunosuppressives in severe extraglandular features ¹³
Progressive systemic sclerosis/diffuse	Fibrosis of skin, vasculopathy, hypertensive renal disease, interstitial lung disease, CREST symptoms	ANA, Scl-70	Symptomatic; ACE-I for renal crisis, various immunosuppressive therapy with varying response
Progressive systemic sclerosis-limited (CREST syndrome)	Calcinosis, Raynaud's, esophageal motility, sclerodacty, telangiectasia, PAH	Anti-centromere antibody	Symptomatic (eg, calcium-channel blockers, proton-pump inhibitor, metoclopramide) PAH: oral anticoagulation; calcium-channel blockers; endothelin receptor antagonist, prostanoids, and epoprostenol in refractory cases ¹⁴
Polymyositis	Idiopathic myositis; weakness of proximal skeletal muscle, increased CPK/aldolase	ANA, anti-Jo-1, anti-PL-7 (anti-threonyl-tRNA synthetase)	Corticosteroids, immunosuppressives (eg, azathioprine, MTX)
Dermatomyositis	Similar to polymyositis but also with dermatologic features: Gottron's papules, heliotrope rash, "mechanic's hands," association with malignancy	ANA, anti-Jo-1, anti-PL-7 (anti-threonyl-tRNA synthetase), anti-Mi-2 antibody (helicase)	Corticosteroids, immunosuppressives (eg, azathioprine, MTX)
Primary biliary cirrhosis	Pruritus, arthritis, hyperpigmentation, hepatomegaly, cholestasis	ANA, anti-mitochondrial antibody, anti-smooth antibody	Corticosteroid, immunosuppressive, ursodiol
Gluten-sensitive enteropathy/celiac sprue	Malabsorption, weight loss, diarrhea, iron deficiency anemia, dermatitis herpetiformis, arthritis	IgA antibody to gliadin and endomysium	Gluten-free diet

INR, International normalized ratio; ANA, antinuclear antibodies; ACE-I, angiotensin-converting enzyme inhibitor; CREST, calcinosis, Raynaud's syndrome, esophageal motility, sclerodacty, telangiectasia; PAH, pulmonary artery hypertension; CPK, creatine phosphokinase; MTX, methotrexate.

combination therapy of cyclophosphamide and steroid. Polyarteritis nodosa-associated hypertension is treated preferably with angiotensin-converting enzyme inhibitor.

Churg-Strauss syndrome/allergic granulomatosis and angiitis. Churg-Strauss syndrome (CSS) is a necrotizing granulomatous vasculitis associated with perinuclear staining anti-neutrophil cytoplasmic antibody (70%) of unknown specificity. It affects men and women equally, with a peak incidence in the 50s. In 5% of cases, CSS has been associated with a use of leukotriene receptor antagonist in patients with steroid-dependent asthma. It is unclear whether the medication or the withdrawal of steroids predisposed these patients to the development of CSS. The presence of 4 or more of the following ACR criteria yields an 85% sensitivity and 99% specificity for diagnosis: asthma, eosinophilia (>10% on the differential or >5000), neuropathy, migratory-transient pulmonary infiltrates, paranasal sinus abnormalities, and biopsy with eosinophils in the extravascular area. In addition, patients can present with palpable purpura, neuropathy, GN,

carditis, increased IgE levels, and hypergammaglobulinemia. Patients are treated with steroids, with the addition of cyclophosphamide in refractory cases.

Large-vessel vasculitis

*Temporal arteritis/giant cell arteritis.*¹¹ Giant cell arteritis (GCA) is a patchy, idiopathic, necrotizing granulomatous vasculitis of medium and large vessels. It is predominantly a disease of the elderly, affecting women more frequently than men. Those with HLA-DR4 and of Northern European ethnicity appear to have a higher predisposition. The presence of 3 or more of the following ACR criteria yields a 94% sensitivity and 91% specificity for diagnosis: age of more than 50 years, localized headache of new onset, temporal artery tenderness, erythrocyte sedimentation rate of greater than 50 mm/h, and biopsy with necrotizing arteritis-granuloma. In addition, patients often present with constitutional symptoms, jaw claudication, visual changes, microscopic hematuria, increased liver function test results, and/or anemia. Up to 50% of

patients can have superimposed polymyalgia rheumatica. Therapy with high-dose steroid should be started promptly if GCA is suspected. Many patients require steroid-sparing agents.

Takayasu's arteritis.¹¹ Takayasu's arteritis is a granulomatous vasculitis of unknown cause affecting predominantly young women, especially Asians. The presence of 3 or more of the following ACR criteria yields a 91% sensitivity and 98% specificity for diagnosis: age less than 40 years, claudication of extremities, decreased brachial artery pulse, blood pressure difference between the extremities of greater than 10 mm Hg, bruit over subclavian artery or aorta, and/or arteriographic narrowing-occlusion of the aorta and its primary branches. Patients are treated similarly to those with GCA.

Kawasaki's syndrome (mucocutaneous lymph node syndrome). Kawasaki's syndrome is the most common vasculitis of childhood, with a peak incidence at the age of 1 year. It is a self-limited, immune-mediated vasculitis of unknown cause with a predilection for Asians. Classically, children present with fever, bilateral conjunctivitis, mucositis, polymorphous rash, lymphadenopathy, and desquamation of palms-soles. Children treated with high-dose aspirin and intravenous immunoglobulin (2 g/kg) within the first 10 days of fever are less likely to have potentially life-threatening coronary artery aneurysm. Unlike other types of vasculitis, steroids are contraindicated because of an association with the development of coronary aneurysm.¹²

CONCLUSION

Autoimmune diseases encompass a wide spectrum of diseases, but all are characterized by alterations in normal immune responsiveness, such that there is a loss of tolerance to particular host constituents reflected by the production of autoantibodies (Table II).^{13,14} Recent research has identified several key changes in components of the immune response (eg, upregulation in proinflammatory cytokines) relevant to the propagation and sustenance of many autoimmune conditions. With this greater understanding of pathogenesis, several novel

immunomodulatory therapies targeting specific components of the inflammatory and immune systems have been introduced into the clinic. This has resulted in improved disease outcomes for patients with a number of autoimmune conditions.

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5. IgE, mast cells, basophils, and eosinophils

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IgE, mast cells, basophils, and eosinophils constitute essential elements in allergic inflammation. Allergen-specific IgE, synthesized in response to allergens in the environment, becomes fixed to FcεRI on the membranes of mast cells and basophils. Aggregation of receptor-bound IgE molecules on re-exposure to specific allergen results in the production of mediators that produce the allergic response. Principal among the cells drawn to sites of mediator release is the eosinophil. (J Allergy Clin Immunol 2006;117:S450-6.)

Key words: IgE, IgE receptor, mast cell, basophil, eosinophil

IgE

IgE (reagenic) antibody shows no transplacental transfer, does not activate complement by the classical pathway, is thermolabile, and will not sensitize after it has been heated to 56°C for several hours. IgE binds with high