Chapter 16
Disruption of Healthy Tissue by the Adaptive Immune Response

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Every autoimmune disease resembles a type II, III, or IV hypersensitivity reaction

Autoimmune disease	Autoantigen	Consequence
Antibody against cell-surface or matrix antigens (type II)		
Autoimmune hemolytic anemia	Rh blood group antigens, I antigen	Destruction of red blood cells by complement and phagocytes, anemia
Autoimmune thrombocytopenia purpura	Platelet integrin gpIIb:IIIa	Abnormal bleeding
Goodpasture's syndrome	Non-collagenous domain of basement membrane collagen type IV	Glomerulonephritis, pulmonary hemorrhage
Pemphigus vulgaris	Epidermal cadherin	Blistering of skin
Pemphigus foliaceus	Desmoglein	Mild blistering of skin
Acute rheumatic fever	Streptococcal cell wall antigens. Antibodies cross-react with cardiac muscle	Arthritis, myocarditis, late scarring of heart valves
Graves' disease	Thyroid-stimulating hormone receptor	Hyperthyroidism
Myasthenia gravis	Acetylcholine receptor	Progressive weakness
Type 2 diabetes (insulin-resistant diabetes)	Insulin receptor (antagonist)	Hyperglycemia, ketoacidosis
Hypoglycemia	Insulin receptor (agonist)	Hypoglycemia

Figure 16.1 A selection of autoimmune diseases, the symptoms they cause, and the autoantigens associated with the immune response. The autoimmune diseases are classified as types II, III, and IV because their tissue-damaging effects are like those of hypersensitivity reactions types II, III, and IV, respectively (see Chapter 14). snRNP, small nuclear ribonucleoprotein; scRNP, small cytoplasmic ribonucleoprotein.

Every autoimmune disease resembles a type II, III, or IV hypersensitivity reaction

Autoimmune disease	Autoantigen	Consequence
Immune-complex disease (type III)		
Subacute bacterial endocarditis	Bacterial antigen	Glomerulonephritis
Mixed essential cryoglobulinemia	Rheumatoid factor IgG complexes (with or without hepatitis C antigens)	Systemic vasculitis
Systemic lupus erythematosus	DNA, histones, ribosomes, snRNP, scRNP	Glomerulonephritis, vasculitis, arthritis

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Every autoimmune disease resembles a type II, III, or IV hypersensitivity reaction

Autoimmune disease	Autoantigen	Consequence
T cell-mediated disease (type IV)		
Type 1 diabetes (insulin-dependent diabetes mellitus)	Pancreatic β-cell antigen	β-cell destruction
Rheumatoid arthritis	Unknown synovial joint antigen	Joint inflammation and destruction
Multiple sclerosis	Myelin basic protein, proteolipid protein	Brain degeneration. Paralysis

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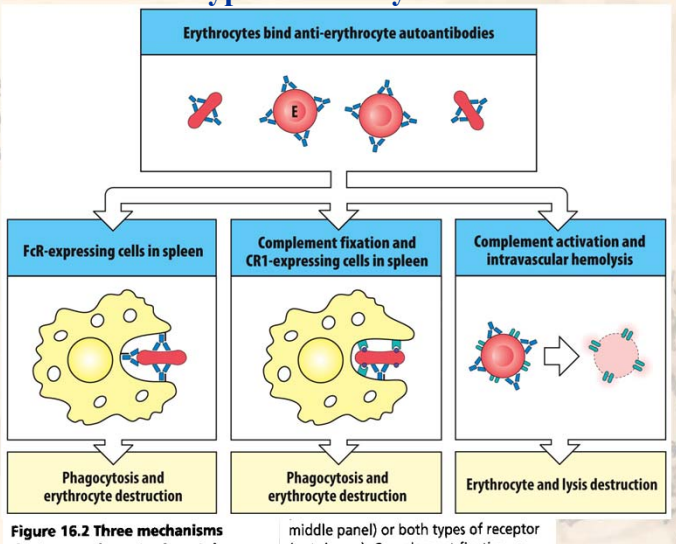
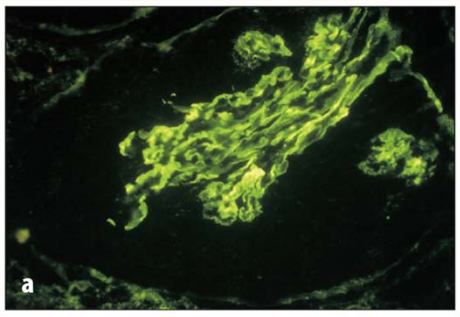


Figure 16.2 Three mechanisms destroy erythrocytes in autoimmune hemolytic anemia. Erythrocytes opsonized with IgG can be bound and engulfed by phagocytes in the spleen that bear an Fcγ receptor (lower left panel) a complement receptor (lower middle panel) or both types of receptor (not shown). Complement fixation on the erythrocyte surface can also lead to complement-mediated lysis of the opsonized erythrocyte.

Every autoimmune disease resembles a type II, III, or IV hypersensitivity reaction



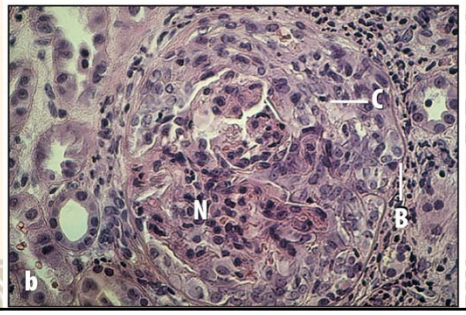


Figure 16.3 Autoantibodies specific for type IV collagen react with the basement membranes of kidney glomeruli, causing Goodpasture's syndrome.

Every autoimmune disease resembles a type II, III, or IV hypersensitivity reaction

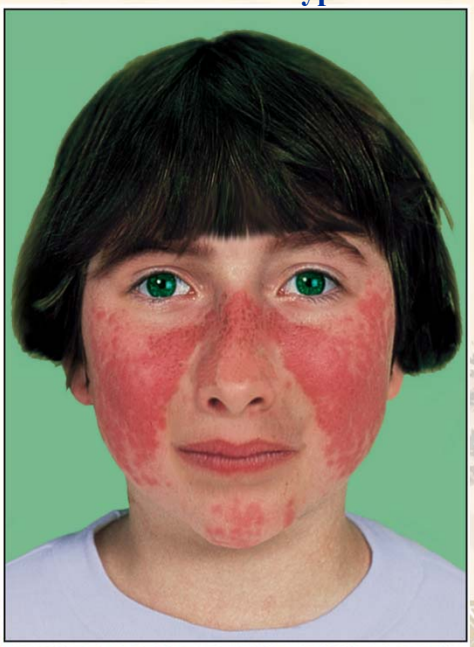


Figure 16.4 The characteristic facial rash of systemic lupus erythematosus. Historically, this butterfly-shaped rash was first used to define and diagnose the disease. Now that the disease is defined immunologically, it is recognized that a proportion of patients who have the disease do not get the rash. Photograph courtesy of M. Walport.

Autoimmune diseases arise when tolerance to self antigens is lost

Mechanisms that contribute to immunological self-tolerance
Negative selection of B cells in the bone marrow
Expression of tissue-specific proteins in the thymus so that they participate in negative selection of T cells
Negative selection of T cells in the thymus
Exclusion of lymphocytes from certain peripheral tissues: brain, eye, testis
Induction of anergy in autoreactive B and T cells that reach the peripheral circulation
Suppression of autoimmune responses by regulatory T cells

Figure 16.5 Mechanisms that contribute to immunological self-tolerance.

Autoimmune diseases arise when tolerance to self antigens is lost

APECED patients suffer a variety of autoimmune diseases and candidiasis

Symptom	Frequency in Finnish patients (%)
Endocrine glands	
Hypoparathyroidism	85
Adrenal failure	72
Ovarian failure	60
Insulin-dependent diabetes mellitus	18
Testicular atrophy	14
Parietal cell atrophy	13
Hypothyroidism	6
Other tissues	
Candidiasis	100
Dental enamel hypoplasia	77
Nail dystrophy	52
Tympanic membrane calcification	33
Alopecia	27
Keratopathy	22
Vitiligo	13
Hepatitis	13
Intestinal malabsorption	10

Figure 16.6 Patients with deficiency of the autoimmune regulator protein AIRE suffer symptoms that are characteristic of a wide range of autoimmune diseases. This condition is called autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) or inherited autoimmune polyglandular disease (APD).

Autoimmune diseases arise when tolerance to self antigens is lost

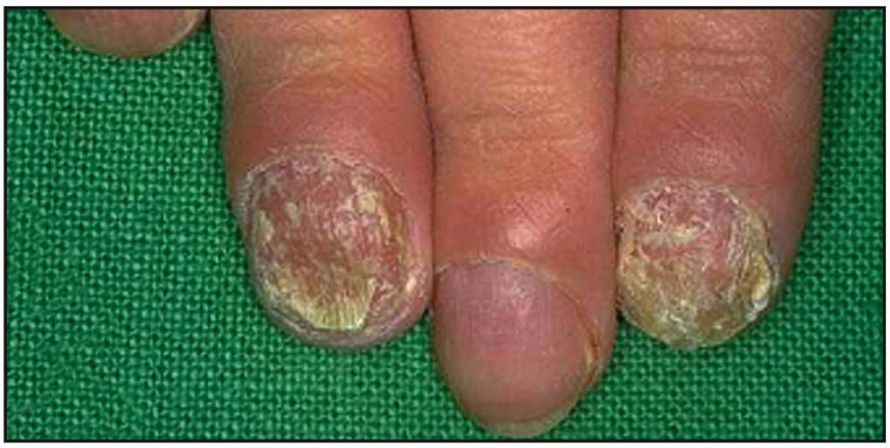


Figure 16.7 Dystrophic fingernails in a patient with APECED. Such visible symptoms of the disease can help in the diagnosis of children with APECED. Photograph courtesy of Mark S. Anderson.

HLA is the dominant genetic factor affecting susceptibility to autoimmune disease

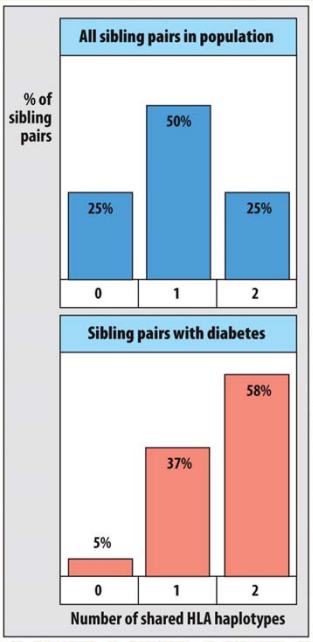


Figure 16.8 Family studies reveal that HLA type correlates with susceptibility to type 1 diabetes. The top panel shows the frequency with which two siblings share HLA haplotypes in the population as a whole. The percentages are those expected from a simple Mendelian segregation of the two maternal and two paternal HLA haplotypes. In the bottom panel the analysis has been confined to pairs of siblings who both have type 1 diabetes. In these sibling pairs, the frequency distribution of HLA haplotypes differs greatly from that expected from simple Mendelian segregation. Pairs of siblings with the disease are much more likely to have the same HLA type than are pairs of siblings who are healthy.

HLA is the dominant genetic factor affecting susceptibility to autoimmune disease

HLA-associated risk factors for autoimmune disease

Disease	HLA allotype	Frequency (%)		Relative risk
		Patients	Control	
Ankylosing spondylitis	B27	> 95	9	> 150
Birdshot chorioretinopathy	A29	> 95	4	> 50
Narcolepsy	DQ6	> 95	33	> 40
Celiac disease	DQ2 and DQ8	95	28	30
Type 1 diabetes	DQ2 and DQ8	81	23	14
Subacute thyroiditis	B35	70	14	14
Multiple sclerosis	DQ6	86	33	12
Rheumatoid arthritis	DR4	81	33	9
Juvenile rheumatoid arthritis	DR8	38	7	8
Psoriasis vulgaris	Cw6	87	33	7
Addison's disease	DR3	69	27	5
Graves' disease	DR3	65	27	4
Myasthenia gravis	DR3	50	27	2
Type 1 diabetes	DQ6	< 0.1	33	0.02

Figure 16.9 Associations of HLA allotypes with autoimmune disease. The data are derived from the Norwegian population. In the column 'Relative risk,' numbers greater than 1 indicate that the HLA allotype confers increased susceptibility relative to the general population; numbers less than 1 indicate increased protection. Data courtesy of Erik Thorsby.

HLA is the dominant genetic factor affecting susceptibility to autoimmune disease

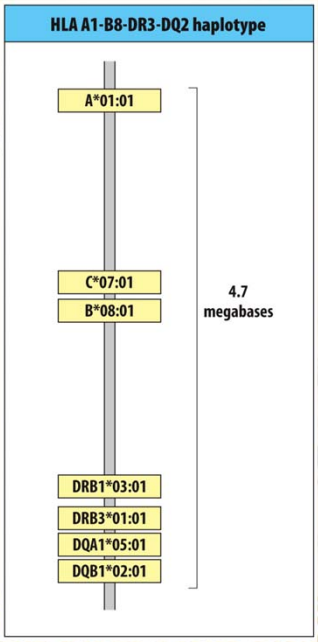


Figure 16.10 Key genes of the A1–B8–DR3–DQ2 HLA haplotype.

HLA is the dominant genetic factor affecting susceptibility to autoimmune disease

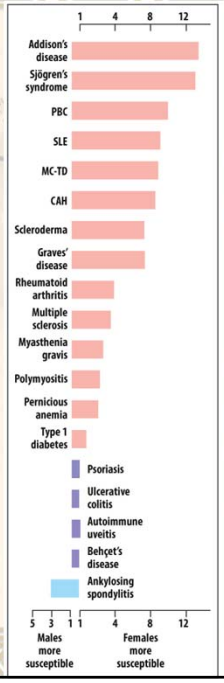


Figure 16.11 Relative incidences of autoimmune disease in females and males. The numbers on the two scales give the ratio of men to women with a disease (on the left) and the ratio of women to men with a disease (on the right). PBC, primary billiary cirrhosis; CAH, chronic active hepatitis; MC-TD, mixed connective tissue disease.

Binding of antibodies to cell-surface receptors causes several autoimmune diseases

Diseases mediated by antibodies against cell-surface receptors				
Syndrome	**Antigen**	**Antibody**	**Consequence**	**Target cell**
Graves' disease	Thyroid-stimulating hormone receptor	Agonist	Hyperthyroidism	Thyroid epithelial cell
Myasthenia gravis	Acetylcholine receptor	Antagonist	Progressive muscle weakness	Muscle
Insulin-resistant diabetes	Insulin receptor	Antagonist	Hyperglycemia, ketoacidosis	All cells
Hypoglycemia	Insulin receptor	Agonist	Hypoglycemia	All cells

Figure 16.12 Diseases mediated by antibodies against cell-surface receptors. Antibodies act as agonists when they stimulate a receptor on binding it, and as antagonists when they block a receptor's function on binding it.

Before blood transfusion, donors and recipients are matched for ABO and the Rhesus D antigens

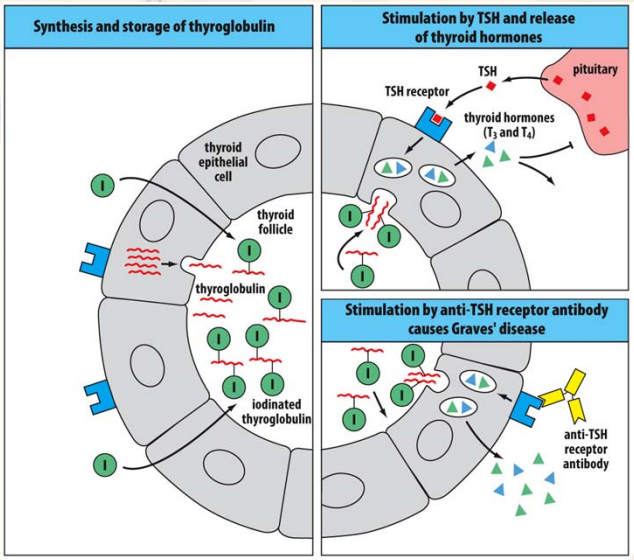


Figure 16.13 Autoantibodies against the TSH receptor cause overproduction of thyroid hormones and Graves' disease. Thyroid epithelial cells make thyroglobulin, a glycoprotein that is stored in follicles formed by the spherical arrangement of thyroid cells. Iodide (green circles) is taken up and used to iodinate and cross-link tyrosine residues of thyroglobulin (left half of the figure). When thyroid hormones are needed. Thyroid-stimulating hormone (TSH) from the pituitary gland binds to the TSH receptor on thyroid cells, inducing the endocytosis and breakdown of iodinated thyroglobulin, with release of the thyroid hormones tri-iodothyronine (T_3) and thyroxine (T_4). As well as regulating metabolism, T_3 and T_4 signal the pituitary to stop releasing TSH (upper right panel). In Graves' disease, autoantibodies bind to the TSH receptor of thyroid cells, mimicking TSH and inducing the continuous synthesis and release of thyroid hormones. In patients with Graves' disease, the production of thyroid hormones becomes independent of the presence of TSH and of the body's requirements for thyroid hormones (lower right panel).

Binding of antibodies to cell-surface receptors causes several autoimmune diseases

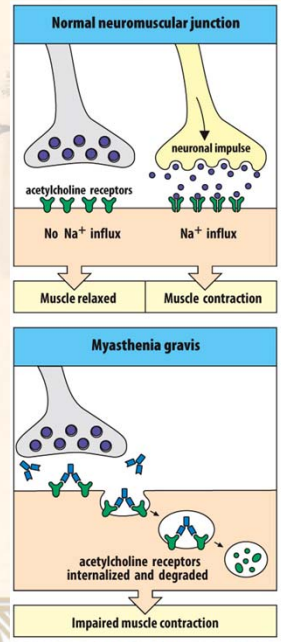


Figure 16.14 Autoantibodies against the acetylcholine receptor cause myasthenia gravis. In a healthy neuromuscular junction, signals generated in nerves cause the release of acetylcholine, which binds to the acetylcholine receptors of the muscle cells, causing an inflow of sodium ions that indirectly causes muscle contraction (upper panel). In patients with myasthenia gravis, autoantibodies specific for the acetylcholine receptor reduce the number of receptors on the muscle-cell surface by binding to the receptors and causing their endocytosis and degradation (lower panel). Consequently, the efficiency of the neuromuscular junction is reduced, which is manifested as muscle weakening.

Binding of antibodies to cell-surface receptors causes several autoimmune diseases

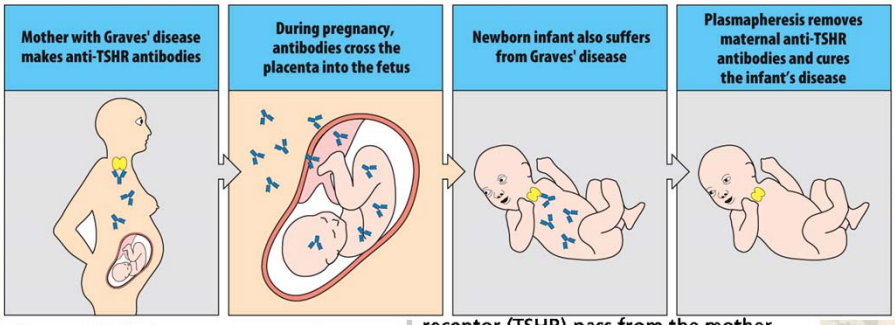


Figure 16.15 Temporary symptoms of antibody-mediated autoimmune diseases can be passed from affected mothers to their newborn babies. The mother has Graves' disease and Graves' ophthalmopathy, which causes her eyes to bulge. IgG autoantibodies against the thyroid-stimulating hormone receptor (TSHR) pass from the mother to the fetus *in utero* and passively give the baby a temporary Graves' disease that disappears with the degradation of maternal IgG in the infant's circulation.

Organized lymphoid tissue sometimes forms at sites inflamed by autoimmune disease

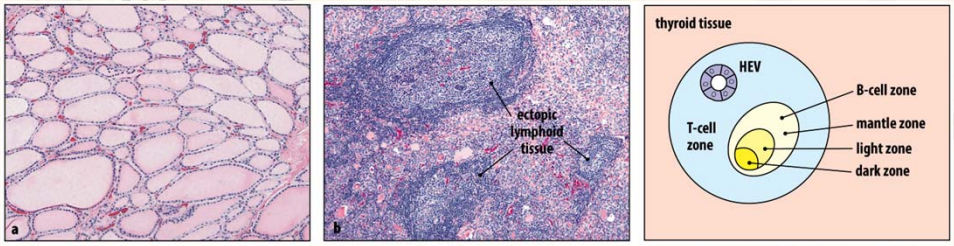


Figure 16.16 Hashimoto's thyroiditis. In a healthy thyroid gland, the epithelial cells form spherical follicles containing thyroglobulin (panel a). In patients with Hashimoto's thyroiditis the thyroid gland becomes infiltrated with lymphocytes, which destroy the normal architecture of the thyroid gland and can become organized into structures resembling secondary lymphoid tissue (panel b), as shown in the schematic diagram at the right. Micrographs courtesy of Yasodha Natkunam.

Organized lymphoid tissue sometimes forms at sites inflamed by autoimmune disease

Autoimmune diseases of endocrine glands	
Thyroid gland	Hashimoto's thyroiditis Graves' disease Subacute thyroiditis Idiopathic hypothyroidism
Islets of Langerhans (pancreas)	Type 1 diabetes (insulin-dependent diabetes, juvenile-onset diabetes) Type 2 diabetes (insulin-resistant diabetes, adult-onset diabetes)
Adrenal gland	Addison's disease

Figure 16.17 Autoimmune diseases of endocrine glands.

The antibody response to an autoantigen can broaden and strengthen by epitope spreading

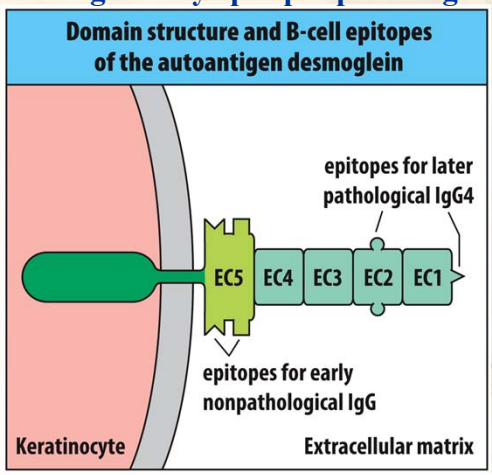


Figure 16.18 Pemphigus foliaceus is a skin blistering disease caused by autoantibodies specific for desmoglein. An adhesion molecule in the cell junctions that hold keratinocytes together, desmoglein is a cell-surface protein with five extracellular domains (EC1–EC5). The autoimmune response starts by making harmless antibodies against the EC5 domain; over time, the response can spread to make antibodies against the EC1 and EC2 domains. These antibodies cause disease and are of the IgG4 isotype.

The antibody response to an autoantigen can broaden and strengthen by epitope spreading

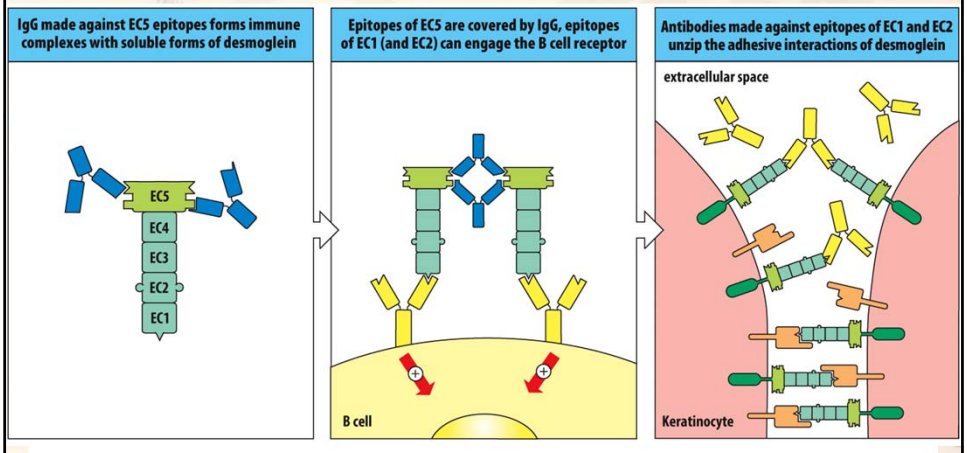


Figure 16.19 How antibodies against desmoglein cause skin blistering. In the early phase of the autoimmune response to desmoglein, antibodies are made against epitopes of the EC5 domain. These epitopes are not accessible to antibody in functional membrane-associated desmoglein, but the antibodies can bind to soluble degradation products of desmoglein (left panel). Soluble immune complexes of antibody desmoglein are bound and processed by B cells specific for epitopes of the EC1 and EC2 domains (center panel). This causes epitope spreading in the later phase of the autoimmune response and the synthesis of high-affinity IgG4 antibodies specific for the EC1 and EC2 epitopes. These epitopes of membrane-associated desmoglein are accessible to antibody, which interferes with the physiological adhesive interactions of desmoglein that are necessary for maintaining skin integrity. Consequently, the antibodies cause the outer layers of the skin to separate, giving blisters (right panel).

Intermolecular epitope spreading occurs in systemic autoimmune disease

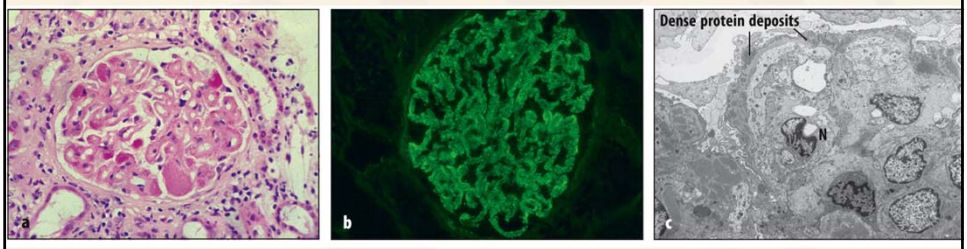


Figure 16.20 Deposition of immune complexes in the kidney glomeruli in systemic lupus erythematosus (SLE). Panel a shows a section through a glomerulus of a patient with SLE. Deposition of immune complexes causes thickening of the basement membrane. In panel b a similar kidney section is stained with fluorescent anti-immunoglobulin antibodies, revealing the presence of immunoglobulin in the basement membrane deposits. Panel c is an electron micrograph of part of a glomerulus. Dense protein deposits are seen between the glomerular basement membrane and the renal epithelial cells. Neutrophils (N) are also present, attracted by the deposited immune complexes. Photographs courtesy of H.T. Cook and M. Kashgarian.

Intermolecular epitope spreading occurs in systemic autoimmune disease

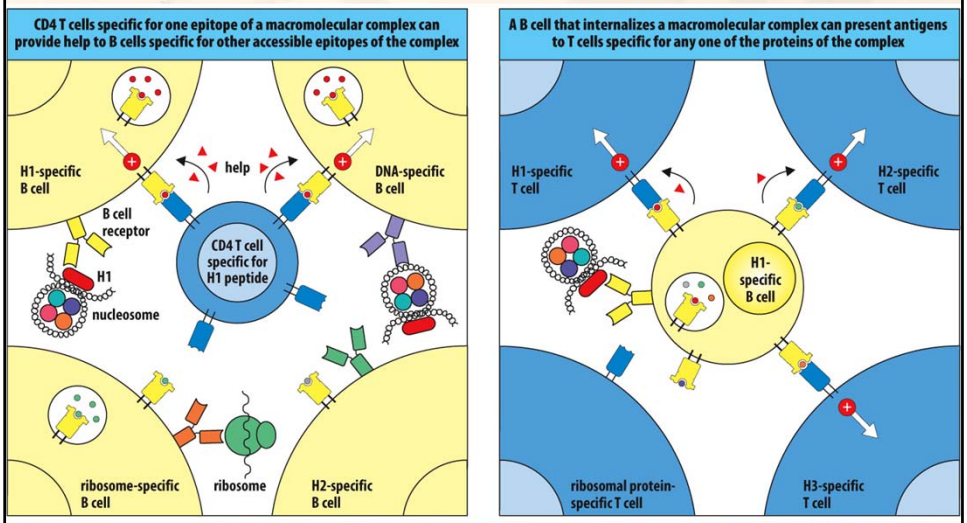


Figure 16.21 In systemic lupus erythematosus (SLE) the immune response in broadened in a antigen-specific manner.

Intravenous immunoglobulin is a therapy for autoimmune diseases

Uses of intravenous immunoglobulin in autoimmune disease		
Benefit	**Disease**	**Symptoms**
Definitely beneficial	Graves' ophthalmopathy	Bulging eyes
	Immune thrombocytopenia	Loss of platelets, bleeding, poor blood clotting
Probably beneficial	Dermatomyositis and polymyositis	Muscle weakness, skin rash
	Autoimmune uveitis	Inflamed eye, blurred vision
Possibly beneficial	Severe rheumatoid arthritis	Joint erosion, pain, loss of mobility
	Type 1 diabetes	Loss of insulin production, severe metabolic disorder
	Systemic lupus erythematosus	Joint pain and swelling, butterfly rash, fatigue
	Post-transfusion purpura	Loss of platelets after a blood transfusion
	Autoimmune neutropenia	Loss of neutrophils, increased susceptibility to infection
	Autoimmune hemolytic anemia	Loss of red blood cells, fatigue
	Autoimmune hemophilia	Bleeding into tissues and joints

Figure 16.22 Intravenous immunoglobulin as a treatment for autoimmune disease. Although there is an extensive literature describing the use of intravenous immunoglobulin as a treatment for autoimmune disease, definitive clinical trials are few and thus the treatment is officially approved for only a few conditions. It is, however, often prescribed 'off label.' Shown here is a summary of autoimmune diseases for which intravenous immunoglobulin treatment is definitely beneficial, probably beneficial, and possibly beneficial.

Intravenous immunoglobulin is a therapy for autoimmune diseases

Functions of intravenous immunoglobulin
Saturates Fc receptors and inhibits Fc receptor-mediated phagocytosis
Saturates FcRn, inhibits recycling of IgG, increases clearance of IgG and reduces its half-life in the blood
Upregulates expression of inhibitory FcγRIIB and further inhibits phagocytosis
Contains anti-idiotypic antibodies that neutralize autoantibodies made by the patient
Suppresses immunoglobulin production including production of autoantibodies
Contains helpful autoantibodies, for example anti-BAFF, that prevent B-cell survival
Downregulates antigen presentation
Attenuates complement activation

Figure 16.23 The immunomodulatory effects of intravenous immunoglobulin.

Monoclonal antibodies that target TNF-α and B cells are used to treat rheumatoid arthritis

Rheumatic diseases caused by autoimmunity
Systemic lupus erythematosus (SLE)
Rheumatoid arthritis
Juvenile arthritis
Sjögren's syndrome
Scleroderma (progressive systemic sclerosis)
Polymyositis–dermatomyositis
Behçet's disease
Ankylosing spondylitis
Reiter's syndrome
Psoriatic arthritis

Figure 16.24 Rheumatic diseases are autoimmune in nature.

Monoclonal antibodies that target TNF-α and B cells are used to treat rheumatoid arthritis

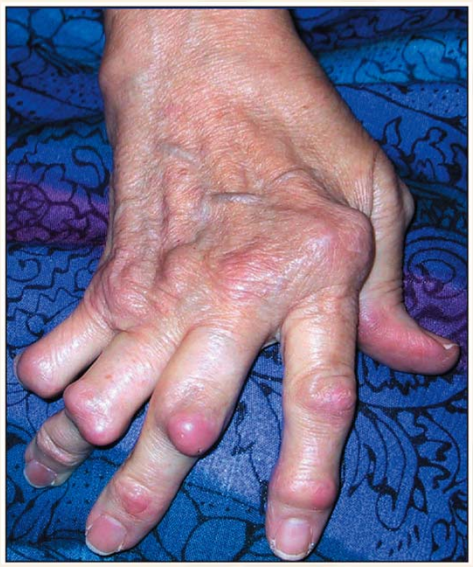


Figure 16.25 Inflamed joints in the hand of a patient with rheumatoid arthritis. Photograph courtesy of J. Cush.

Monoclonal antibodies that target TNF-α and B cells are used to treat rheumatoid arthritis

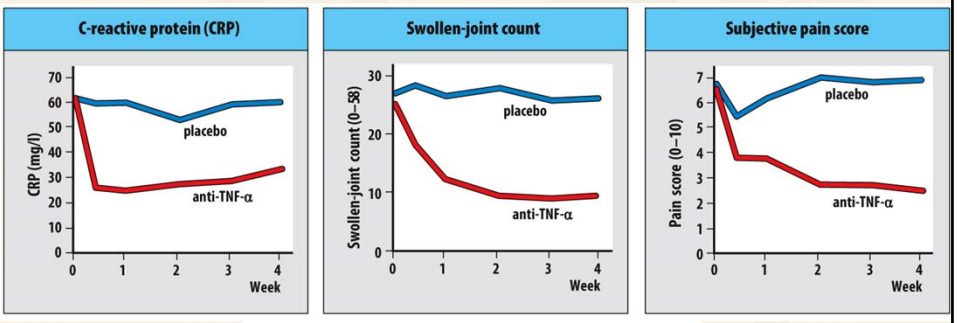


Figure 16.26 The effects of treatment of rheumatoid arthritis with anti-TNF-α. For each parameter measured (level of C-reactive protein, swollen joints, and pain), the values for patients given a placebo treatment are depicted by the blue curve and the values for patients treated with anti-TNF-α antibody are depicted by the red curve.

Rheumatoid arthritis is influenced by genetic and environmental factors

*DRB1*04* allele	Amino acid position in DRβ chain		
	67	70	71
**04:01*	L	Q	K
**04:02*	I	D	E
**04:04*	L	Q	R
**04:05*	L	Q	K
**04:08*	L	Q	R

Figure 16.27 Basic residues in the peptide-binding groove of the DRβ*04 chain are necessary to confer susceptibility to rheumatoid arthritis. With the exception of *DRB1*04:02*, all the *DRB1*04* alleles shown are associated with susceptibility to rheumatoid arthritis. What distinguishes the DRβ*04:02 chain from those encoded by the other alleles is a cluster of amino acid substitutions at positions 67, 70, and 71. These substitutions change the localized charge environment within the peptide-binding groove by removing a basic (positively charged) residue (shown in blue) and inserting two acidic (negatively charged) residues (shown in red).

Rheumatoid arthritis is influenced by genetic and environmental factors

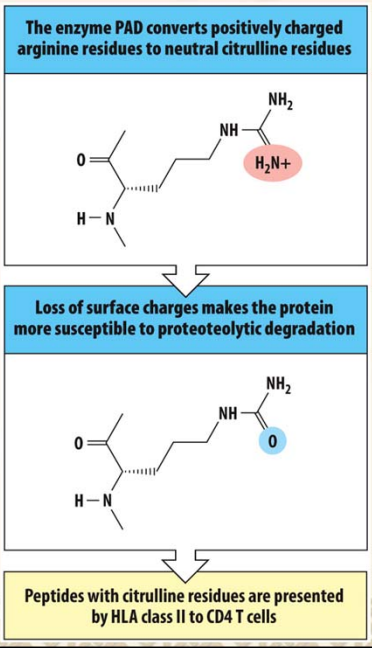


Figure 16.28 The enzyme peptidyl arginine deiminase converts the arginine residues of tissue proteins to citrulline. In tissues stressed by wounds or infection, peptidyl arginine deaminase (PAD) activity is induced. By converting arginine residues to citrulline, PAD destabilizes proteins and makes them more susceptible to degradation. It also introduces novel B-cell and T-cell epitopes into tissue proteins that can stimulate an autoimmune response.

Rheumatoid arthritis is influenced by genetic and environmental factors

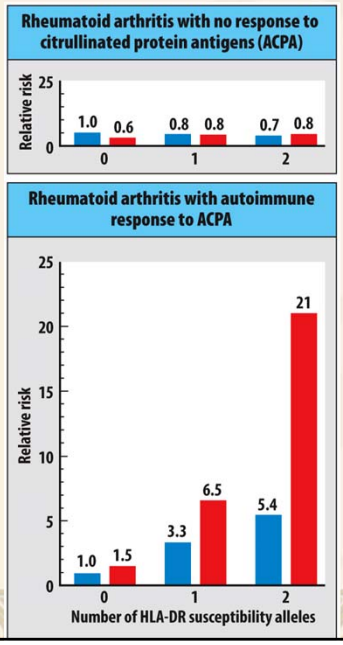


Figure 16.29 Patients with rheumatoid arthritis form two distinct groups. Upper panel: the relative risk of developing rheumatoid arthritis in which no autoimmune response to citrullinated protein antigens (ACPA) is made does not correlate with the presence of *HLA-DRB1*04* 'susceptibility' alleles or with smoking. The red columns indicate smokers, the blue columns nonsmokers. The number above each column is the relative risk of disease for that group. Lower panel: in contrast, the relative risk of developing rheumatoid arthritis in which an autoimmune response to ACPA has been made is increased by the presence of *HLA-DRB1*04* susceptibility alleles and by smoking. At highest risk are smokers who have any two *HLA-DRB1*04* susceptibility alleles (see Figure 16.27). These data are from a cohort of Swedish patients with rheumatoid arthritis. Data courtesy of Lars Klareskog.

Autoimmune disease can be an adverse side-effect of an immune response to infection

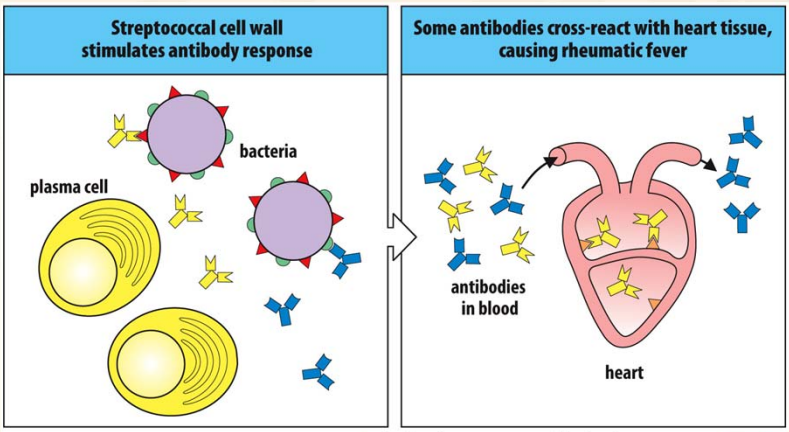


Figure 16.30 Antibodies against streptococcal cell-wall antigens cross-react with antigens on heart tissue. The immune response to the bacteria produces antibodies against various epitopes of the bacterial cell surface. Some of these antibodies (yellow) cross-react with the heart, whereas others (blue) do not. An epitope in the heart (orange) is structurally similar, but not identical, to a bacterial epitope (red).

Autoimmune disease can be an adverse side-effect of an immune response to infection

Associations of infection with autoimmunity

Infection	HLA association	Consequence
Group A *Streptococcus*	Not known	Rheumatic fever (carditis, polyarthritis)
Chlamydia trachomatis	HLA-B27	Reiter's syndrome (arthritis)
Shigella flexneri, *Salmonella typhimurium*, *Salmonella enteritidis*, *Yersinia enterocolitica*, *Campylobacter jejuni*	HLA-B27	Reactive arthritis
Borrelia burgdorferi	HLA-DR2, DR4	Chronic arthritis in Lyme disease
Coxsackie A virus, Coxsackie B virus, echoviruses, rubella	HLA-DQ2, HLA-DQ8 DR4	Type 1 diabetes

Figure 16.31 Infections associated with the start of autoimmunity. Lyme disease, a form of arthritis, is caused by *Borrelia* bacteria that are transmitted from rodents to humans by tick bites of the type shown on the opening page of this chapter.

Noninfectious environmental factors affect the development of autoimmune disease

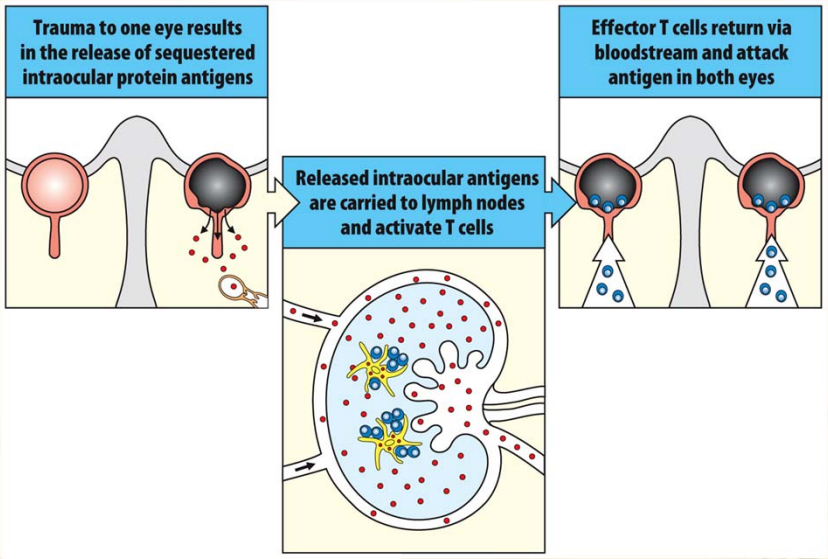


Figure 16.32 Physical trauma to one eye initiates autoimmunity that can destroy vision in both eyes.

Type 1 diabetes is caused by the selective destruction of insulin-producing cells in the pancreas

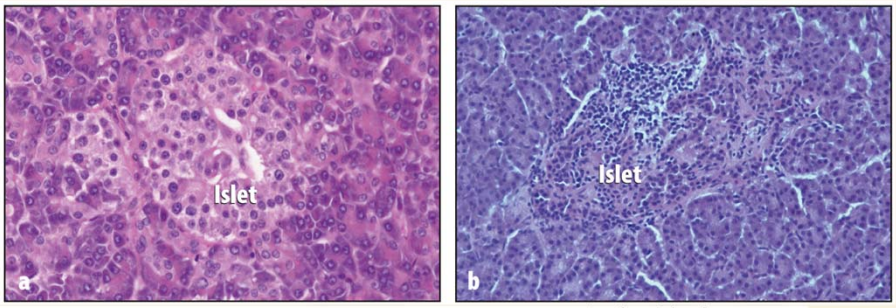


Figure 16.33 Comparison of histological sections of a pancreas from a healthy person and a patient with type 1 diabetes. Panel a is a micrograph of healthy human pancreas, showing a single islet. The islet is the discrete light-staining area in the center of the photograph. It is composed of hormone-producing cells, including the β cells that produce insulin. Panel b shows a micrograph of an islet from a patient with acute onset of type 1 diabetes. The islet shows insulitis, an infiltration of lymphocytes from the islet periphery toward the center. The lymphocytes are the clusters of cells with darkly staining nuclei. Both tissue sections are stained with hematoxylin and eosin; magnification ×250. Photographs courtesy of G. Klöppel.

Combinations of HLA class II allotypes confer susceptibility and resistance to type 1 diabetes

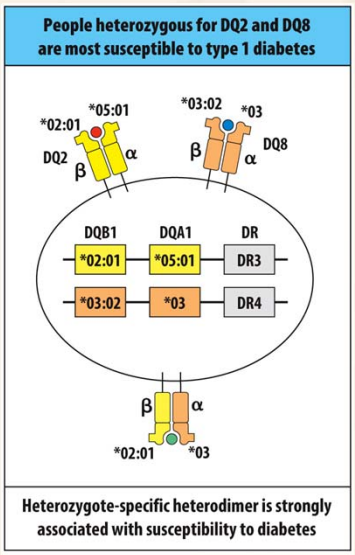


Figure 16.34 Certain HLA heterozygous individuals are more susceptible to diabetes than homozygous individuals. The person shown here has two HLA haplotypes that are independently associated with susceptibility to type 1 diabetes. The *DR3* haplotype contains *DQ* genes that encode the DQα*05:01 chain and the DQβ*02:01 chain; the *DR4* haplotype contains genes that encode the DQα*03 chain and the DQβ*03:02 chain. The two α chains and two β chains made in this person's cells can associate in different combinations to form four different DQ isoforms, of which three (those shown in the figure) are associated with susceptibility to diabetes. The DQ heterodimer associated with the highest susceptibility is that comprising the DQα*03 chain made from the *DR4* haplotype and the DQβ*02:01 chain made from the *DR3* haplotype. This heterodimer can be made only in *DR3/DR4* heterozygous individuals, whereas the two heterodimers with weaker disease association are also made in homozygous individuals: heterodimers of the DQα*05:01 and DQβ*02:01 chains (called the DQ2 molecule) in *DR3* haplotype homozygotes and heterodimers of the DQα*03 and DQβ*03:02 chains (called the DQ8 molecule) in *DR4* haplotype homozygotes. The heterozygote is therefore more susceptible to disease than either homozygote. As a general rule, heterozygosity gives increased fitness over homozygosity, but in this situation the reverse is true.

Combinations of HLA class II allotypes confer susceptibility and resistance to type 1 diabetes

Risk of type 1 diabetes	HLA locus			Amino acid position in DRβ chain			
	DQB1	*DQA1*	*DRB1*	67	71	74	86
Protective	*03:02 / *02:01	*03 / *05:01	*04:03 / *03	L	R	E	V
Moderate	*03:02 / *02:01	*03 / *05:01	*04:04 / *03	L	R	A	V
High	*03:02 / *02:01	*03 / *05:01	*04:05 / *03	L	R	A	G
High	*03:02 / *02:01	*03 / *05:01	*04:01 / *03	L	K	A	G

Figure 16.35 HLA-DR4 subtypes modify the susceptibility to type 1 diabetes conferred by the DQα*03:DQβ*0201 heterodimer. The leftmost panels show the risk of type 1 diabetes for individuals having the haplotype combinations shown in the adjacent column. All four individuals are heterozygotes for *DR3* and *DR4* haplotypes and make the DQα*03:DQβ*02:01 heterodimer. These individuals have different *DRB1*04* alleles, as indicated by the colored boxes. The amino acid substitutions that distinguish the four DRβ*04 chains are shown on the right. The common amino acid residue at each position is shown in gray; the rarer residue is highlighted in black. The associated HLA-DR4 subtype modifies the risk of type 1 diabetes conferred by DQα*03:DQβ*02:01 in qualitative and quantitative ways.

Celiac disease is a hypersensitivity to food that has much in common with autoimmune disease

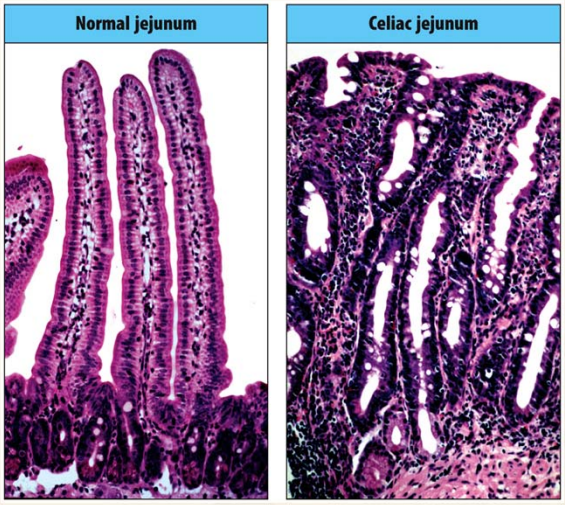


Figure 16.36 Comparison of healthy and celiac intestinal mucosa. Left: the surface of the normal small intestine is folded into finger-like villi, which provide an extensive surface for nutrient absorption. Right: in celiac disease the inflammation and immune response damage the villi. There is lengthening and increased cell division in the underlying crypts to produce new epithelial cells. There are greater numbers of lymphocytes in the epithelial layer and an increase in effector CD4 T cells, plasma cells, and macrophages in the lamina propria. The damage to the villi reduces the person's ability to utilize food and can cause life-threatening malabsorption and diarrhea. Right photograph courtesy of Allan Mowat.

Celiac disease is a hypersensitivity to food that has much in common with autoimmune disease

	Immune mechanism								
Type of disease	MHC class II molecules	Auto-antibodies	T_H1 type immunity	Post-translational modifications	Type I IFN	IL-15	IL-21	NK-cell receptors	Conserved MHC class I molecules
Celiac disease									
Rheumatoid arthritis									
Type 1 diabetes									
Multiple sclerosis									
Autoimmune thyroiditis									
Systemic lupus erythematosus									
Primary biliary cirrhosis									
Psoriasis or psoriatic arthritis									
Inflammatory bowel disease									

Evidence for involvement | Unclear evidence for involvement | No evidence for involvement

Figure 16.37 Shared characteristics of the immune mechanisms causing celiac diseases and autoimmune diseases.

Celiac disease is caused by the selective destruction of intestinal epithelial cells

DQ2		DQ8		Relative risk of celiac disease
DQB1*02	DQA1*05	DQB1*03	DQA1*03	
+	+	+	+	High
+ +	+			High
		+	+	Medium
+	+			Medium
+ +				Medium
+				Low
	+			Very low
				Very low

Figure 16.38 Comparison of genotypes and risk for celiac disease. Shown here are how various combinations of two DQα chains and two DQβ chains give genotypes with a range of relative risk for celiac disease.

Celiac disease is caused by the selective destruction of intestinal epithelial cells

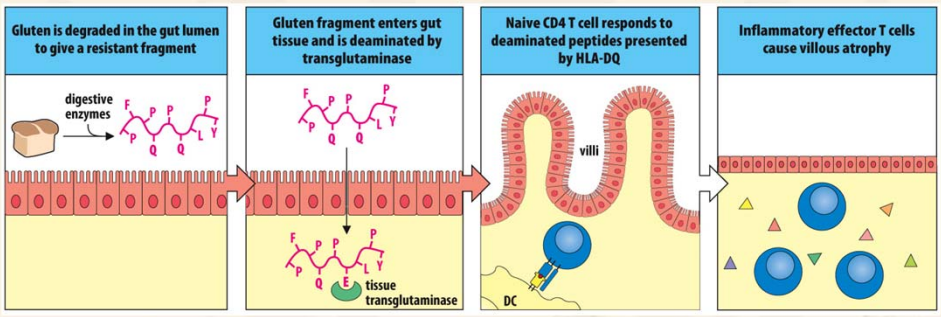


Figure 16.39 The mechanism of celiac disease. In celiac disease, inflammation of the small intestine is caused by a CD4 T-cell response. The T cells are specific for gluten-derived peptides that have been deaminated by tissue transaminase and presented by HLA-DQ8 or HLA-DQ2 molecules. Only part of the peptide epitope is shown. DC, dendritic cell.

Senescence of the thymus and the T-cell population contributes to autoimmunity

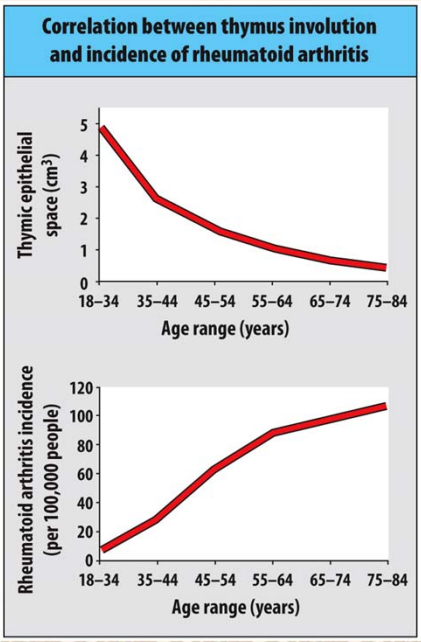


Figure 16.40 Correlation between thymus involution and rheumatoid arthritis. With age there is an inverse correlation between the decreasing capacity of the thymus to make new T cells and the increasing incidence of rheumatoid arthritis. Data courtesy of C.M. Weyand and J.J. Goronzy.

Autoinflammatory diseases of innate immunity

Disease	Protein	Dominant (D)/ Recessive (R)	Skin rash	Arthritis	Other
Familial Mediterranean fever	Pyrin	R	+	+	SAA amyloidosis
TNF receptor-associated periodic syndrome	TNF-receptor 1, (CD120a)	D	+	+	SAA amyloidosis
Hyper-IgD syndrome	Mevalonate kinase	R	+	+	Lymph node involvement
Familial cold autoinflammatory syndrome 1	NLRP3 (cryopyrin)	D	+	+	Occular inflammation
Blau syndrome	NOD2	D	+	+	Occular inflammation
Majeed syndrome	Lipin-2	R	+	+	Osteomyelitis
Familial cold autoinflammatory syndrome 2	NLRP12	D	+	+	Early childhood onset
Deficiency of IL-1-receptor agonist	IL-1 receptor agonist	R	+	+	Lymph node involvement
Pyogenic arthritis, pyodema gangrenosum and acne syndrome	CD2 binding protein 1	D	+	+	Early childhood onset
Early-onset enterocolitis (inflammatory bowel syndrome)	IL-10 receptor α IL-10 receptor β	R	+	–	Early infancy onset
Joint contractures, muscle atrophy, macrocytic anemia and panniculitis-induced lipodystrophy syndrome	Proteasome subunit β5i	R	+	+	Chronic

Figure 16.41 Autoinflammatory diseases that have been associated with mutation and variation of genes contributing to innate immunity and inflammation.

Summary

Hypersensitivity reaction	Allergy	Transplantation	Autoimmunity
Type I	Peanut	–	–
Type II	Chronic urticaria	Hyperacute rejection	Autoimmune hemolytic anemia
Type III	Serum sickness	Chronic rejection	Systemic lupus erythematosus
Type IV	Poison ivy	Acute rejection	Type 1 diabetes

Figure 16.42 Comparison of allergy, transplantation, and autoimmunity. Allergic diseases, the diseases arising from transplantation, and autoimmune diseases all involve effector mechanisms that correspond to the type II, III, and IV hypersensitivity reactions. Unique to allergic disease is the type I hypersensitivity reaction mediated by IgE.