DEFINITIONS AND TYPES OF AUTOIMMUNITY

Autoimmunity versus Autoimmune Disease

The classic studies of Paul Ehrlich in the early twentieth century laid the foundation for our current notions of the concept of autoimmunity. Ehrlich used the term autoimmunity to signify an immune response against self and introduced the phrase horror autotoxicus, suggesting that there are mechanisms to protect against autoimmunity. Over the years, autoimmunity has been recognized as not uncommon and not necessarily detrimental. Thus, an important distinction must be drawn between autoimmunity, which may be asymptomatic, and autoimmune disease, which occurs when autoimmunity leads to an inflammatory response, resulting in tissue injury. An autoimmune response does not necessarily imply the existence of autoimmune disease.

T-Cell versus B-Cell-Mediated Autoimmune Diseases

Autoimmune disease may be mediated primarily by T cells, as in multiple sclerosis or the animal model experimental autoimmune encephalomyelitis (EAE). In that case, disease can be transmitted from one animal to another by transferring antigen-specific T lymphocytes. Alternatively, autoimmune disease may be caused by B cells that produce autoantibodies, as in the case of systemic lupus erythematosus (SLE). Autoantibodies bind to self-antigens (proteins, nucleic acids, or other molecules from one’s own body, also known as autoantigens) and can damage cells either by binding directly to a cell surface or extracellular matrix antigen or through the formation of immune complexes (see the section “Mechanisms of Autoimmune Tissue Injury and Examples”). Autoantibody-mediated autoimmune diseases sometimes can be transmitted transplacentally, as in the case of neonatal Graves’ disease or congenital complete heart block and neonatal lupus. IgG antibodies/autoantibodies can cross the placenta, whereas IgM cannot. Thus, neonatal autoimmune diseases are invariably caused by IgG, not IgM, autoantibodies. In view of the half-life of IgG (twenty-one to twenty-eight days), nearly all maternal IgG disappears from the circulation of the baby by six to twelve months postpartum. Thus, in most cases, neonatal autoimmune disease is transient. One exception is congenital complete heart block, which is thought to be mediated by the transplacental passage of anti-Ro or La autoantibodies, which may cross-react with cardiac antigens, causing permanent inflammation-mediated damage to the cardiac conduction system.
**Systemic versus Organ-Specific Autoimmune Disease**

Autoimmune disease also can be classified as systemic or organ specific. Systemic autoimmune diseases, such as SLE, involve multiple organs or tissues, whereas organ-specific autoimmune diseases involve a single organ or tissue, such as the thyroid gland in autoimmune thyroiditis or the islets of Langerhans in type I diabetes. Some of the more common systemic and organ-specific autoimmune diseases are listed in Table 6.1.

**MECHANISMS OF AUTOIMMUNE TISSUE INJURY AND EXAMPLES**

Tissue damage in autoimmune diseases can occur through several mechanisms, which are analogous to three of the classical types of hypersensitivity reactions: type II (caused by autoantibodies reactive with cell surface or matrix antigens), type III (caused by immune complexes), and type IV (delayed-type hypersensitivity, mediated by T cells).

**Type II Autoimmune Reactions**

Type II hypersensitivity reactions are caused by antibodies against altered self-proteins, such as penicillin–protein conjugates. In the case of autoimmunity, antibodies generated either against cell surface antigens/extracellular matrix proteins are cytotoxic (type IIA) or else they have agonistic/antagonistic properties (type IIB). Autoantibodies to cell surface antigens may initiate cell destruction by complement-mediated lysis (cell destruction), phagocytosis, or antibody-dependent cell-mediated cytotoxicity (ADCC). Examples include autoimmune hemolytic anemia, and autoimmune thrombocytopenia (Table 6.1). Some autoantibodies bind to surface receptors, either activating (e.g., anti-TSH receptor autoantibodies in Graves’ disease) or inhibiting (e.g., anti-acetylcholine antibodies in myasthenia gravis) their function.

**Type IIA Autoimmune Reaction: Autoimmune Hemolytic Anemia**

Autoimmune hemolytic anemia (AIHA) is an example of type IIA autoimmunity. In this disorder, a self-antigen on the surface of erythrocytes elicits an autoantibody response, resulting in the binding of autoantibody to the erythrocyte surface followed by destruction of the antibody-coated erythrocytes by the reticuloendothelial system of the spleen and liver. The mechanism of hemolysis depends on the type of autoantibodies. Autoimmune hemolysis is classified into two groups on the basis of thermal reactivity of the autoantibodies. Warm autoantibodies react optimally at temperatures of 35°C–40°C, whereas cold agglutinins and other cold-reactive autoantibodies react maximally at 4°C. Warm autoantibodies are typically polyclonal IgG but may also be IgM or IgA. Most are IgG1 subclass antibodies reactive with Rh antigens. These antibodies are detected by the direct antiglobulin (Coombs) test (Figure 6.1A). Erythrophagocytosis mediated by Fc receptors on Kupffer cells in the liver and macrophages in the splenic marginal zone is generally the major mechanism of erythrocyte destruction in patients with warm autoantibodies.

In contrast, AIHA induced by cold agglutinins is complement mediated. These autoantibodies are of the IgM class and cannot interact with Fc receptors.
### Table 6.1 Some Human Autoimmune Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Organ(s) Involved</th>
<th>Prevalence per 100,000&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Female: Male Ratio</th>
<th>Autoantibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic autoimmune diseases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Joints, skin, nervous system, kidneys, blood cells, heart, lungs</td>
<td>24</td>
<td>9:1</td>
<td>Anti-dsDNA&lt;sup&gt;b&lt;/sup&gt; Anti-Sm&lt;sup&gt;b&lt;/sup&gt; Anti-ribosomal P&lt;sup&gt;b&lt;/sup&gt; Anti-RNA helicase&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Joints, blood vessels, lungs</td>
<td>860</td>
<td>3:1</td>
<td>Anti-citrullinated peptides&lt;sup&gt;b&lt;/sup&gt; Rheumatoid factor</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>Exocrine glands (salivary and lacrimal glands), kidneys, nerves</td>
<td>14</td>
<td>9:1</td>
<td>Anti-Ro60 (SS-A) Anti-Ro52 Anti-La (SS-B)</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>Skin, blood vessels, GI tract, lungs, kidneys</td>
<td>4</td>
<td>4:1</td>
<td>Anti-topoisomerase I&lt;sup&gt;b&lt;/sup&gt; Anti-fibrillarin (U3 RNP)&lt;sup&gt;b&lt;/sup&gt; Anti-RNA polymerase I&lt;sup&gt;b&lt;/sup&gt; Anti-RNA polymerase III&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>Muscles, lungs</td>
<td>5</td>
<td>2:1</td>
<td>tRNA synthetases (histidyl, alanyl, threonyl, glycy1, etc.)&lt;sup&gt;b&lt;/sup&gt; Signal recognition particle&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Organ-specific autoimmune diseases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis</td>
<td>Thyroid</td>
<td>982</td>
<td>9:1</td>
<td>Thyroid peroxidase Thyroglobulin</td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>Thyroid</td>
<td>1152</td>
<td>9:1</td>
<td>Thyroid-stimulating hormone receptor</td>
</tr>
<tr>
<td>Addison’s disease</td>
<td>Adrenal glands</td>
<td>5</td>
<td>9:1</td>
<td>Glutamic acid dehydrogenase, insulin, other islet cell antigens</td>
</tr>
<tr>
<td>Type I diabetes</td>
<td>Pancreatic islet cells</td>
<td>192</td>
<td>1:1</td>
<td>Desmoglein 3</td>
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<tr>
<td>Pemphigus vulgaris</td>
<td>Skin</td>
<td>N/A</td>
<td>N/A</td>
<td>230 kDa hemidesmosomal antigen</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>Skin</td>
<td>N/A</td>
<td>N/A</td>
<td>Unknown melanocyte antigens</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>Skin melanocytes</td>
<td>400</td>
<td>1:1</td>
<td>Type VII collagen</td>
</tr>
<tr>
<td>Goodpasture’s syndrome</td>
<td>Kidneys, lungs</td>
<td>0.05</td>
<td>1:1</td>
<td></td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Nervous system</td>
<td>5</td>
<td>2:1</td>
<td>Acetylcholine receptor</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Nervous system</td>
<td>58</td>
<td>2:1</td>
<td>Unknown myelin antigens</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>Gastric parietal cells</td>
<td>151</td>
<td>2:1</td>
<td>Parietal cell antigens, intrinsic factor</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>Bile ducts</td>
<td>N/A</td>
<td>N/A</td>
<td>Dihydrolipoamide acyltransferase and other antigens&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>Liver</td>
<td>0.4</td>
<td>9:1</td>
<td>Smooth muscle antigens (F-actin)</td>
</tr>
</tbody>
</table>

(continued)
Table 6.1 (continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Organ(s) Involved</th>
<th>Prevalence per 100,000(^a)</th>
<th>Female: male ratio</th>
<th>Autoantibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenic purpura</td>
<td>Platelets</td>
<td>N/A</td>
<td>3:1</td>
<td>Antiplatelet antibodies against GPIIbIIIa and/or the GPIb(\alpha) complex</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>Erythrocytes</td>
<td>N/A</td>
<td>~1.5:1</td>
<td>Rh, i, i, and other antigens</td>
</tr>
</tbody>
</table>

N/A, not available.
\(^a\) USA, 1996 estimate; \(^b\) disease specific autoantibodies.

because there are no Fc receptors capable of binding the \(\mu\) heavy chain. Idiopathic cold agglutinin disease generally is associated with an IgM paraprotein against the “I” antigen, an erythrocyte surface protein. Unlike IgG, which must be cross-linked, pentavalent IgM fixes complement efficiently without cross-linking. After binding to the erythrocyte’s surface at low temperature, IgM cold agglutinins activate C1, C4, C2, and C3b. With rewarming, the antibody can dissociate, but C3b remains fixed irreversibly, which can lead to recruitment of the terminal complement components (C5–C9, membrane attack complex) and intravascular hemolysis or C3b receptor-mediated phagocytosis by reticuloendothelial cells.

Case 1. Autoimmune Hemolytic Anemia, a Type II Autoimmune Reaction

A twenty-eight-year-old woman with a four-year history of systemic lupus erythematosus (SLE) presented for a scheduled follow-up in clinic. Because she avoids the sun and started taking hydroxychloroquine four years ago, her rash and arthritis improved, but over the past six months, she had become progressively more fatigued and began to notice dark urine. Review of medications, alcohol intake, recreational drug use, and sick contacts was unrevealing. On physical exam, she was mildly tachycardic at 105, with a two out of six systolic ejection murmur at the left sternal border, dullness to percussion over Traube’s space (the normally resonant gastric bubble), and a palpable spleen tip.

Her hemoglobin was 9.5 mg/dl (normal 12–16 mg/dl), mean cell volume (MCV, a measure of erythrocyte size) was normal at 88 cu \(\mu\)m, and platelets were 75,000/ml (normal 140–400,000/ml).
Urinalysis revealed no blood but was remarkable for urobilinogen of 8 mg/dl (normal <2 mg/dl). Hepatic panel was notable for a total bilirubin of 2 mg/dl (normal <1.5 mg/dl) with indirect bilirubin of 1.5 mg/dl (normal <0.8 mg/dl) and direct bilirubin 0.5 mg/dl (normal <0.7 mg/dl). Lactate dehydrogenase (LDH) was elevated at 350 IU/L (normal <250 IU/L), and corrected reticulocyte count (immature erythrocytes) was 3 percent (normal <1 percent).

Direct Coombs test was positive (Figure 6.1A). Haptoglobin (a scavenger of free hemoglobin) was reduced to <5 mmol/L (normal 10–30 mmol/L). Parvovirus B19, TSH, vitamin B12 level, folate level, iron profile, and ferritin were unremarkable. A review of her blood smear showed numerous spherocytes (spherical erythrocytes instead of the usual biconcave disc shape, the result of damage to the red cell membrane as it passes through the spleen; Figure 6.1B) and confirmed thrombocytopenia (low numbers of platelets). An ultrasound of her abdomen revealed a normal liver but an enlarged spleen.

On the basis of these clinical findings, the diagnoses of autoimmune hemolytic anemia and thrombocytopenia were made. She was treated with prednisone (a corticosteroid) at a dose of 60 mg/day. Initially, her platelet count improves to 120,000. However, after three months of treatment, her anemia did not improve. She gained twenty pounds and noted easy bruising, fatigue, and difficulty sleeping as well as “feeling on edge all the time.” Since she had not improved and was experiencing side effects of prednisone, she was given a pneumococcal pneumonia vaccination before surgery to remove her spleen. After splenectomy her anemia, thrombocytopenia, and some of her fatigue resolved. After tapering the prednisone dose, she “felt normal.” Two years later, her symptoms recurred and laboratory tests confirmed evidence of active hemolytic anemia. A liver-spleen scan indicated the presence of an accessory spleen (present in 10–30 percent of normal population), which was removed. She is currently symptom free.

**COMMENT**

Autoimmune hemolytic anemia in patients with SLE is usually due to the presence of warm-reactive autoantibodies against the Rh antigen. As the autoantibody-coated erythrocytes pass through the spleen, phagocytes bearing Fc receptors remove some of the immunoglobulin on the cell surface along with some of the cell membrane, which subsequently reseals, causing the erythrocyte to take the form of a spherocyte. Eventually, the erythrocyte is unable to be repaired and is removed from the circulation. If this occurs faster than new erythrocytes can be produced (normal life span of an erythrocyte is about 120 days) then anemia develops. The elevated indirect bilirubin (a measure of bilirubin before the liver has a chance to process it) is a result of the increased breakdown of hemoglobin.

Autoimmune hemolytic anemia can occur in a variety of circumstances, including neoplastic diseases (most often lymphomas), connective tissue diseases (such as SLE), and infections (viral, bacterial, or mycoplasma). Or it may be drug induced (classically penicillin). The initial treatment is to diagnose and treat the underlying cause or
remove offending agents. If this is not possible, corticosteroids such as prednisone are often used. If patients do not respond then consideration is given to the use of cytotoxic drugs (e.g., azathioprine or vincristine) or splenectomy.

**Type IIB Hypersensitivity: Graves’ Disease**

Graves’ disease is an organ-specific autoimmune disease of the thyroid mediated by stimulatory (agonistic) autoantibodies. Autoantibodies to the thyroid-stimulating hormone receptor (TSHR) cause hyperthyroidism in patients with Graves’ disease. The pathogenicity of anti-TSHR autoantibodies is demonstrated by the occurrence of neonatal Graves’ disease after passive transplacental transfer of IgG thyroid-stimulating autoantibodies from a mother with Graves’ disease to the fetus. The anti-TSHR autoantibodies in Graves’ disease inhibit binding of TSH to its receptor by binding to a conformational epitope (the part of the antigen recognized by an antibody) of the extracellular domain of the TSHR. Although the autoantibodies appear to interact with TSHR somewhat differently than the natural ligand, they nevertheless stimulate TSHR signaling, causing increased production of thyroid hormone.

**Type IIB Hypersensitivity: Myasthenia Gravis**

Myasthenia gravis is an autoimmune disease caused by inhibitory (antagonistic) autoantibodies that bind and block the acetylcholine receptor (AChR), causing muscular weakness and fatigue. The AChR is found at postsynaptic membranes of neuromuscular junctions and binds acetylcholine released from a nerve ending, transiently opening a calcium channel. The signal is terminated by acetylcholine esterase, an enzyme located in the basal lamina between the nerve ending and the postsynaptic membrane. As in mothers with Graves’ disease, transplacental passage of IgG autoantibodies from mothers with myasthenia gravis can cause transient neonatal myasthenia gravis. Anti-AChR autoantibodies cause disease by down-regulating expression of the receptor and by complement-mediated lysis of the cells bearing the AChR. Intermolecular cross-linking of AChR by the autoantibodies may lead to antigenic modulation.

**Type III Autoimmune Reactions (Immune Complex Disease)**

Autoantibodies also cause disease by forming networks of autoantibodies bound to their antigens (immune complexes). The antigen-antibody complexes can deposit in tissues, causing inflammatory lesions. Studies of serum sickness led to the first description of an immune complex disease. Serum sickness is manifested by fever, glomerulonephritis, vasculitis, urticaria, and arthritis, appearing seven to twenty-one days after primary immunization or two to four days after secondary immunization with a foreign protein. Two consequences of immune complex formation are complement fixation and binding to Fc or complement receptors on phagocytes. Clearance is facilitated by the binding of immune complexes to C3b receptors (CR1) on erythrocytes, which retain the complexes in the circulation until their removal by the reticuloendothelial cells of the spleen or liver.

Immune complex formation is a normal process, which removes foreign antigens from the circulation. Removal of
immune complexes by phagocytes bearing Fc or complement receptors prevents their deposition at other sites. The efficiency of uptake of immune complexes by either Fc receptors or CR1 is proportional to the number of IgG molecules associated with the complex.

Immune complexes can activate either the classical or the alternative complement pathway. The classical pathway plays a major role in maintaining immune complexes in a soluble form, preventing their deposition in tissues. C3b bound to the solubilized immune complexes promotes their clearance by the erythrocyte complement receptor CR1. If the rate of immune complex formation exceeds the ability to clear these complexes via Fc receptors and CR1, the immune complexes can deposit within tissues, leading to inflammation. This efficient immune complex transport and removal by Fc and complement receptors can be overwhelmed, however, leading to tissue deposition and immune complex disease. This situation may result from overproduction of immune complexes, blockade of phagocytosis by the reticuloendothelial system, or complement depletion resulting in inefficient solubilization of immune complexes.

Systemic lupus erythematosus is the prototype of human immune complex disease. Tissue damage in lupus is mainly caused by immune complexes containing autoantibodies to soluble antigens. These autoantibodies include antibodies against RNA-protein complexes (e.g., anti-Sm, RNP, Ro/SS-A, and La/SS-B antibodies) and DNA-protein complexes (e.g., anti-double-stranded DNA, antihistone, antichromatin antibodies). The target antigens are found mainly in the cell nucleus, although in some cases (e.g., antiribosomal antibodies), they may be cytoplasmic. Immune complexes containing these autoantibodies, especially anti-double-stranded DNA antibodies, are selectively enriched in the renal glomeruli (capillary tufts that produce urine as an ultrafiltrate of blood) of patients with lupus nephritis and are thought to play a critical role in establishing the inflammatory response. Immune complex deposition in the kidney leads to proliferative glomerulonephritis and effacement of the normal glomerular architecture (Figure 6.2). As is the case in serum sickness, active lupus nephritis is frequently associated with hypocomplementemia (Figure 6.2). In addition to the kidneys (glomeruli), immunoglobulin and complement deposits are found in the blood vessels (vasculitis), skin (rashes), nervous system, and other locations. Preformed immune complexes may become trapped in the glomerular filter, or immune complexes may develop in situ because of the interaction of cationic antigens (e.g., histones) with heparan sulfate glycosaminoglycan in the glomerular basement membrane. The association of lupus with deficiencies of the early classical complement components, especially C2 and C4, is consistent with the role of complement pathways in solubilizing immune complexes (see the section “Pathogenesis of Autoimmune Disease”).

Case 2. Systemic Lupus Erythematosus, a Type III Autoimmune Reaction

A fifteen-year-old girl developed myalgias (muscle pain), painful and swollen joints, and low-grade fevers and was found to have a positive antinuclear antibodies (ANA) test. Kidney function was normal. She was given a diagnosis of SLE and treated with hydroxychloroquine (an antimalarial), azathioprine (a nucleoside analog), and 10 mg/day
Three years later, she developed alopecia (hair loss) and a red, ulcerating rash of the legs. A skin biopsy was reported to be “consistent with lupus.” The skin lesions resolved when the dose of prednisone was increased. For the next five years, her lupus remained well controlled with hydroxychloroquine and intermittent low-dose prednisone until she moved to another state and was unable to continue her health insurance. Several months after stopping all of her medications, vasculitic skin lesions recurred on the legs, and she developed a rash on the face (Figure 6.2A). Laboratory testing revealed that her creatinine (a measure of renal function) was now abnormally elevated at 3.4 mg/dl (normal 1.0 mg/dl), her albumin was low,
and her urine tested positive for protein (proteinuria, >300 mg/dl) and blood (hematuria). Microscopic examination revealed seven erythrocytes per high power field. Fluorescent antinuclear antibody testing was positive at a titer of 1:640 homogeneous pattern and antidi double-stranded (ds) DNA antibodies were detected at a titer of 1:160 using the *Crithidia luciliae* kinetoplast staining assay (Figure 6.2B, 6.2C). Complement components C3 and C4 were low (56 and 11 mg/dl, respectively). She was treated with a high dose of methylprednisolone (another corticosteroid) intravenously. A renal biopsy was performed and showed proliferative lupus nephritis (Figure 6.2D). Immunofluorescence showed staining of the glomerular basement membrane for IgG (Figure 6.2E) as well as IgM and C3. She was treated with mycophenolate mofetil (MMF, 1,500 mg twice a day), and after four months, her proteinuria and hematuria resolved, the creatinine returned to near baseline (1.1 mg/dL), C4 increased to 85 mg/dl, and anti-dsDNA antibodies decreased to 1:20 (Figure 6.2F).

**COMMENT**

Systemic lupus erythematosus is the prototype of human immune complex disease. For reasons that are unclear, autoantibodies against double-stranded DNA are involved in the formation of immune complexes that appear to be particularly prone to become trapped in the renal glomeruli, where they can cause inflammation (glomerulonephritis). The levels of anti-dsDNA often are low during periods of disease quiescence. In this case, a flare of disease activity was precipitated by stopping medications that keep the autoimmune response in check (prednisone and hydroxychloroquine), leading to the production of high levels of anti-dsDNA antibodies that could be detected by staining the kinetoplast (a circular DNA molecule) of *Crithidia luciliae* organisms. These autoantibodies formed immune complexes, resulting in the consumption of classical complement components C3 and C4 (the classic inverse relationship between anti-DNA and complement levels, as illustrated in Figure 6.2F). Because the immune complexes were inadequately cleared, they deposited in the renal glomeruli, resulting in the patient’s new onset hematuria and proteinuria and the decline in her renal function (increased creatinine). With re-institution of appropriate therapy, the anti-DNA levels declined, C3 and C4 levels recovered, and renal immune complex deposition diminished, resulting in an improvement of renal function.

**Type IV Autoimmune Reactions (T-Cell Mediated)**

Type IV hypersensitivity reactions are mediated by T cells that recognize peptides presented on the surface of antigen-presenting cells in the context of class II major histocompatibility complex (MHC) molecules and that produce the cytokines interferon γ (IFN-γ), interleukin 3 (IL-3), tumor necrosis factor (TNF) α, TNF-β, and granulocyte-macrophage colony-stimulating factor (GM-CSF). These cells constitute a subset of T helper cells termed TH1 (T helper 1) cells. Elaboration of “TH1 cytokines” leads to macrophage recruitment and activation, enhanced expression of adhesion molecules, and increased...
production of monocytes by the bone marrow. Delayed-type hypersensitivity in response to the intradermal injection of certain antigens, such as tuberculin (used for tuberculosis skin testing), is a classic example of a type IV hypersensitivity reaction. In the case of autoimmunity, self-antigens (instead of foreign antigens) plus MHC molecules are recognized by the antigen receptors of the TH1 cells. Examples of type IV autoimmune reactions include insulin-dependent diabetes mellitus (pancreatic antigens, such as glutamic acid dehydrogenase, insulin, and other islet cell antigens are recognized), multiple sclerosis (unidentified components of myelin are recognized), experimental allergic encephalomyelitis (an animal model of multiple sclerosis in which myelin basic protein is recognized), and Hashimoto’s thyroiditis (thyroid antigens such as thyroid peroxidase and thyroglobulin are recognized).

**Case 3. Hashimoto’s Thyroiditis: A Type IV Autoimmune Disease**

A thirty-one-year-old woman was seen in the clinic because she had a sensation that something was stuck in her throat. Her older sister had a similar problem. She also noted feeling tired and had gained weight since giving birth to a child five years earlier. Her hair and skin seemed to be getting drier. On examination, her thyroid gland was mildly enlarged on palpation (Figure 6.3A, 6.3B) and ultrasound revealed multiple small nodules and a pseudonodule indicated by the arrow (Figure 6.3C). A needle biopsy of the thyroid revealed a diffuse interstitial lymphocytic infiltrate with formation of lymphoid follicles (Figure 6.3D). Residual thyroid follicles were small, and some contained inspissated colloid. Complete blood count was notable for mild anemia (hemoglobin 11.3 g/dl). Her T4 level was low (1.9 mg/dl), thyroid-stimulating hormone (TSH) level was elevated at 25 mIU/L, and serum antithyroid peroxidase and antithyroglobulin autoantibodies were detected. Antithyroid-stimulating hormone receptor antibody was negative. She was given a diagnosis of autoimmune (Hashimoto’s) thyroiditis on the basis of the low T4 level, elevated TSH, and the autoantibody profile and was treated with thyroid replacement. Her TSH levels normalized and the anemia resolved and she noted a gradual decrease in her fatigue. Her skin and hair dryness improved.

**COMMENT**

Pathologically Hashimoto’s thyroiditis represents an infiltration of the thyroid gland with T and B lymphocytes, which often organize to form germinal centers (Figure 6.3D). The lymphocytic infiltration may be visualized on positron emission tomography (PET) scanning as shown in Figure 6.3E. Patients with Hashimoto’s thyroiditis may exhibit a focal or diffusely increased 2-[^18F]fluoro-2-deoxy-D-glucose (FDG) uptake, which correlates with the T-/B-cell infiltration. The B cells make antibodies against thyroid antigens, as seen in this patient, whereas the T cells produce cytokines that stimulate the B cells and induce the thyroid cells to undergo apoptosis (programmed death). Eventually, the thyroid is destroyed and is unable to secrete thyroid hormone, resulting in hypothyroidism. The diffusely micronodular appearance on ultrasound (Figure 6.3C) is due to disruption of the normal microarchitecture of the thyroid gland. The small nodules
seen on ultrasound ("pseudonodules") represent germinal centers and areas of focal infiltration in the gland, such as shown in Figure 6.3D.

There may be overlap with Graves’ disease, which is manifested by agonistic (activating) antibodies reactive with the thyroid-stimulating hormone receptor (see class II autoimmune reactions). Initially, this antibody may activate the thyroid into oversecretion of thyroid hormone (seen as increased levels of T4), leading to hyperthyroidism. Eventually, this too may cause destruction of the thyroid gland, resulting in a hypothyroid state.

The cause of Hashimoto’s thyroiditis is unknown. There are familial linkages (as seen in this patient). Other conditions that may predispose to Hashimoto’s are physical stress, radiation, viral infections, increased iodine,
medications (most notably amiodarone, lithium, and interferon-α), other autoimmune diseases (most notably Sjögren’s syndrome), female gender, and pregnancy.

Epidemiology of Autoimmune Disease

There are nearly 100 different forms of autoimmune disease, making these disorders a major cause of chronic illness, affecting up to 3 percent of the general population. Nearly any organ can be affected by either systemic or organ-specific autoimmune disease (Table 6.1). Women make up nearly 75 percent of all individuals afflicted by autoimmune disease, making these disorders one of the ten leading causes of death in women less than sixty-five years old. However, the female-to-male ratio varies widely among different diseases, being as high as 9:1 in SLE, Sjögren’s syndrome, and autoimmune thyroiditis and as low as 1:1 in type I diabetes, Goodpasture’s syndrome, and vitiligo (Table 6.1). The mean age of onset also varies widely, with some disorders typically occurring early in childhood (e.g., type I diabetes, juvenile rheumatoid arthritis), others in the childbearing years (ages 15–45, e.g., SLE), and still others in later life (e.g., Sjögren’s syndrome). There may be striking ethnic/racial predispositions to autoimmune disease. For example, SLE is about three times more prevalent in individuals of African, Asian, or Latin ancestry than in individuals of European ancestry, whereas Sjögren’s syndrome and multiple sclerosis are more prevalent in those of European ancestry. The racial/ethnic differences are likely to reflect differences in the frequencies of disease susceptibility genes. The costs of these disorders to society are enormous. Rheumatoid arthritis affects 2.1 million Americans (1.5 million women and 600,000 men) at an annual cost of about $6,000 per patient (direct medical costs and indirect costs such as absence from work). Lupus affects 500,000 Americans at an estimated annual cost of $13,000 per patient, a total $6.5 billion per year.

ANIMAL MODELS OF AUTOIMMUNE DISEASE

The difficulty in carrying out randomized, well-controlled research in patients complicates studies of the pathogenesis and treatment of human autoimmune disease. Often the simplest course is to first study the disease in an appropriate animal model. However, because animal models of disease rarely are identical to the human disorder, the suitability of a particular model in any given situation must be considered carefully before undertaking animal studies. The list of animal models of autoimmune disease is extensive, and only some of the more commonly studied models can be reviewed here (see also Table 6.2).

SLE (NZB X NZW F1, MRL, BXSB, TMPD)

Numerous mouse strains have been studied over the years as animal models of SLE. Some strains develop lupus spontaneously, such as NZB×NZW (F1) (NZB/W) hybrid mice, MRL mice, and BXSB male mice. Other models, such as tetramethylpentadecane (TMPD, pristane) induced lupus, are inducible with chemicals. The spontaneous models afford hope that if the genetic defect(s) responsible for lupus-like disease in these mice can be identified, similar defects will be found in human lupus. However, the inducible TMPD
### Table 6.2 Key Features of Selected Animal Models of Autoimmune Disease

<table>
<thead>
<tr>
<th>Animal Model</th>
<th>Disease</th>
<th>Susceptible Strains</th>
<th>Similarities to Human Disease</th>
<th>Differences from Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>(NZBxNZW)F1</td>
<td>SLE</td>
<td>N/A</td>
<td>Glomerulonephritis, ANA, anti-dsDNA, female &gt; male</td>
<td>Autoantibody profile, no vasculitis</td>
</tr>
<tr>
<td>MRL lpr/lpr</td>
<td>SLE (RA)</td>
<td>N/A</td>
<td>Lymphadenopathy, glomerulonephritis, erosive arthritis, vasculitis, female &gt; male</td>
<td>Fas deficiency causes mainly hematological autoimmunity in humans</td>
</tr>
<tr>
<td>BXSB male</td>
<td>SLE</td>
<td>N/A</td>
<td>Glomerulonephritis</td>
<td>Only male is affected, limited autoantibody profile</td>
</tr>
<tr>
<td>TMPD-induced lupus</td>
<td>SLE (RA)</td>
<td>BALB/c, C57BL/6, SJL, DBA/1, DBA/2, 129Sv, and most others</td>
<td>Glomerulonephritis, erosive arthritis, pulmonary vasculitis, ANA, anti-dsDNA, anti-Sm/RNP, female &gt; male, increased interferon α/β</td>
<td>Not genetically mediated (but influenced by the genetic background)</td>
</tr>
<tr>
<td>Collagen-induced arthritis</td>
<td>RA</td>
<td>DBA/1 and others</td>
<td>Chronic, erosive inflammation of peripheral joints</td>
<td>Induced by immunization. In mice, males have a greater susceptibility. Primarily affect ankles than knees</td>
</tr>
<tr>
<td>TTP deficiency</td>
<td>RA</td>
<td>129Sv</td>
<td>Erosive, polyarticular symmetrical arthritis</td>
<td>Patchy alopecia, dermatitis, conjunctivitis, and “kangaroo” hunched posture</td>
</tr>
<tr>
<td>K/BxN</td>
<td>RA</td>
<td>BALB/c and others</td>
<td>Erosive, polyarticular symmetrical arthritis</td>
<td>Induced by autoantibodies; no RF or anti-CCP antibodies</td>
</tr>
<tr>
<td>EAE</td>
<td>MS</td>
<td>SJL and others</td>
<td>Relapsing-remitting or chronic-progressive, highly variable neurological disorder</td>
<td>Inducible instead of developing spontaneously, might require adjuvants</td>
</tr>
<tr>
<td>NOD</td>
<td>TID</td>
<td>N/A</td>
<td>Insulin-dependent diabetes</td>
<td>Autoimmune sialadenitis, autoimmune thyroiditis, autoimmune peripheral polynephropathy, SLE-like disease, and prostatitis</td>
</tr>
</tbody>
</table>

MS, multiple sclerosis; N/A, not applicable; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TID, type I diabetes.
model more closely mimics the abnormalities in interferon (IFN) α and β production seen in most lupus patients.

NZB/W F1 MODEL
The NZB/W model was the first murine model of lupus nephritis. New Zealand Black (NZB) mice develop autoimmune hemolytic anemia and the female New Zealand White (NZW) mice develop mesangial glomerulonephritis late in life. In contrast, the F1 hybrid (NZB/W) develops early onset severe (proliferative, immune complex-mediated) glomerulonephritis along with antinuclear antibodies (ANA), antichromatin, and anti-dsDNA antibodies. However, these mice lack other classic clinical and serological manifestations of SLE, such as arthritis, inflammatory skin rashes, serositis, and anti-Sm autoantibodies. Extensive genetic analysis of this strain has revealed three major susceptibility intervals on chromosomes 1, 4, and 7. Each of these intervals appears to contain multiple-disease susceptibility genes and several candidate genes have been identified. NZB/W mice have been used widely for preclinical studies of various therapeutic interventions for lupus nephritis.

MRL MODEL
MRL mice, an inbred strain derived from several other strains, develop antinuclear antibodies and late onset glomerulonephritis reminiscent of SLE. A spontaneously occurring mutation led to impressive lymphoproliferation (lpr mutation), severe, early onset nephritis closely resembling proliferative lupus nephritis, the development of erosive arthritis (more characteristic of rheumatoid arthritis than SLE), salivary gland inflammation (reminiscent of Sjögren’s syndrome), vasculitis, and skin disease resembling cutaneous lupus. Both MRL and MRL lpr/lpr mice develop a host of autoantibodies characteristic of SLE, including anti-Sm and anti-dsDNA as well as severe hypergammaglobulinemia. These autoantibodies develop earlier in the presence of the lpr mutation, which generally accelerates the onset of lupus-like disease in this strain. The abnormalities caused by the lpr mutation are due to an ETn retrotransposon insertion into the Fas gene, which encodes an important protein mediator of apoptosis. Defective apoptosis of lymphocytes leads to the accumulation of CD3⁺CD4⁻CD8⁻ (“double negative”) T cells, accounting for the massive lymphoproliferation seen in MRL lpr/lpr mice.

BXSB MODEL
This strain was created by crossing male SB/Le and female C57BL/6J mice. Male, but not female, BXSB mice develop severe glomerulonephritis, lymphadenopathy, splenomegaly, autoimmune hemolytic anemia, and anti-dsDNA autoantibodies. Thus, the sex predilection is an important difference from human lupus and most other murine lupus models. A mutant gene located on the Y chromosome, designated Yaa (Y chromosome-linked autoimmune acceleration), causes accelerated lupus-like disease in male BXSB mice. A recent study showed that the Yaa mutation results from translocation of a 4-megabase portion of the X chromosome to the Y chromosome, leading to increased expression of several genes that are normally X linked, including TLR7.

TMPD-INDUCED LUPUS
Intraperitoneal injection of pristane (2, 6, 10, 14 tetramethylpentadecane, TMPD) can induce a lupus-like syndrome in non-autoimmune-prone mice characterized by proliferative glomerulonephritis, erosive arthritis, pulmonary vasculitis, and a
variety of lupus autoantibodies, including anti-dsDNA and anti-Sm. All or nearly all immunocompetent mouse strains are susceptible to lupus induced by this hydrocarbon oil. This inducible model of lupus is, at least so far, unique in reproducing the increased levels of IFN-α and IFN-β seen in the majority of lupus patients. The disease is largely abrogated in type I interferon receptor deficient mice.

**Rheumatoid Arthritis (Collagen-Induced Arthritis, TTP Deficiency, K/BxN Model)**

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by prominent joint involvement. Arthritis is typically associated with erosions of cartilage and subchondral bone, formation of an inflammatory tissue, consisting of activated macrophages, T cells, fibroblasts, and other immune cells (pannus). This can ultimately result in joint destruction and significant joint deformities. In addition to the joints, RA can cause vasculitis, splenomegaly, and leukopenia (Felty’s syndrome), interstitial lung disease, and other abnormalities. Rheumatoid factor (an autoantibody against the Fc portion of immunoglobulin) and antibodies against citrulline-modified proteins or peptides (usually detected as antibodies against an artificially produced cyclic citrullinated peptide, or CCP) are typical serological findings in RA, although not all patients exhibit these abnormalities. Several animal models of RA exist, but they do not precisely reproduce the clinical and laboratory abnormalities.

**Collagen-Induced Arthritis (CIA)**

Immunization of susceptible rodent strains with type II collagen (CII) leads to the development of a severe polyarticular arthritis resembling human rheumatoid arthritis. Although induced by heterologous CII, immunization leads to a response against autologous CII. CIA can be induced in susceptible strains of mice, rats, and primates. Histologically, both RA and CIA are characterized by an intense synovitis accompanied by erosions of cartilage and subchondral bone by a pannuslike tissue. Unlike human RA, CIA is monophasic. In addition, there are important serological differences. In general, rheumatoid factor is not produced in CIA and antibodies against cyclic citrullinated peptide (CCP) are absent.

**TTP Deficiency**

Tristetraprolin (TTP) is a transcription factor that can bind to and destabilize mRNAs encoding TNF-α and granulocyte-macrophage colony-stimulating factor (GM-CSF). Mice deficient in TTP develop a complex syndrome characterized by cachexia, polyarticular arthritis, dermatitis, autoimmunity, and myeloid hyperplasia accompanied by extramedullary hematopoiesis (erythrocyte production outside of the bone marrow). TTP knockout mice exhibit exuberant inflammatory pannus and bony erosions. These mice also produce high titers of anti-DNA, and antinuclear antibodies; however, rheumatoid factors are absent.

**K/BxN Model**

Although RA has been considered primarily a type IV autoimmune reaction for many years, the finding that autoantibodies against glucose-6-phosphate isomerase (GPI) can transfer RA-like joint disease to normal mice has rekindled interest in the possibility that antibody-mediated autoimmune mechanisms (type II or type III) could play a role in the pathogenesis of
RA. K/BxN T-cell-receptor transgenic mice express a transgenic T-cell receptor specific for a peptide of the ubiquitously expressed self-protein GPI. Arthritis in this model is initiated by antibodies against GPI. The resulting synovitis is chronic, erosive, and associated with pannus formation. Paradoxically, although the GPI antigen is ubiquitous, autoimmunity is focused on the joints. It appears that the GPI protein, not a cross-reactive synovial antigen, is the target of the pathogenic antibodies. Although the histological appearance of the affected joints is reminiscent of RA, there is no evidence that RA in humans can be caused by antibodies against GPI. The classic serological abnormalities, rheumatoid factor, and anti-CCP antibodies are not seen, and anti-TNF-α antibodies have little effect in this model.

Multiple Sclerosis (Experimental Allergic Encephalomyelitis)

Multiple sclerosis is a chronic autoimmune disease affecting the central nervous system, including the brain and spinal cord. The disease affects about 350,000 Americans and about 1.1 million worldwide. Age of onset is typically twenty to forty years old, women are affected more frequently than men (2:1 ratio), and it is most prevalent in individuals of northern European ancestry. It is thought to be mediated primarily by a T-cell-mediated attack on the myelin sheaths of certain nerve fibers, resulting in inflammation, demyelination, and gliosis (scarring). In addition, autoantibodies against components of myelin such as myelin oligodendrocyte glycoprotein (MOG) may be seen and also may contribute to disease pathogenesis by fixing complement. During the course of disease, the lesions classically occur at different times and in different locations. Symptoms include sensory loss, paresthesias (numbness, tingling), visual changes due to optic neuritis, tremor, ataxia, weakness, spasticity, and other neurological symptoms. Patients with multiple sclerosis can exhibit either a relapsing-remitting or a progressive course.

Experimental autoimmune encephalomyelitis (EAE) is a model of multiple sclerosis induced in susceptible animals by immunization by intact myelin or components of myelin, the sheath that surrounds certain neurons. Like CIA for RA, EAE can be induced in several species, including mice, rats, guinea pigs, rabbits, and primates. Although induced by heterologous antigen(s), the disease is autoimmune. Several proteins have been used to induce EAE, including myelin basic protein (MBP), proteolipid protein (PLP), and MOG. Different antigens cause somewhat different clinical manifestations. By administering the antigen with complete Freund’s adjuvant and pertussis toxin, the blood-brain barrier is disrupted permitting access by immune cells. The resulting demyelinating disease closely resembles human multiple sclerosis and is thought to be mediated primarily by T cells because disease can be transferred to normal animals by T cells (type IV autoimmune reaction). There is only limited evidence that an immune response to MBP, PLP, or MOG is involved in human disease, and it is hypothesized that other myelin antigens may be the targets of autoreactive T cells in MS.

Type I Diabetes (Nonobese Diabetic Mouse Model)

Type I diabetes (TID) is an autoimmune disease in which the insulin producing β cells in the pancreatic islets of Langerhans
are gradually destroyed by autoreactive T cells over a period of months to years. After about 80 percent of the islet cells are destroyed, insulin deficiency and a severe form of insulin-dependent diabetes marked by ketoacidosis develop. The disease usually affects children and young adults but can occur at any age. Males and females are affected equally. The highest incidence is in Scandinavians (35 per 100,000 per year). Individuals with a genetic susceptibility to the disease are thought to develop autoimmunity in response to an undefined environmental trigger. Most patients with TID produce anti-islet cell autoantibodies reactive with insulin, glutamic acid decarboxylase, ICA-512/IA-2, phogrin, or other antigens. These autoantibodies generally appear before the onset of clinical diabetes and have been used for early diagnosis of the condition.

The nonobese diabetic (NOD) mouse is the most useful model of autoimmune type I diabetes. NOD mice spontaneously develop marked infiltration of T cells into the pancreatic islets. The infiltrating T cells selectively destroy the pancreatic β cells. In addition to diabetes, NOD mice spontaneously develop autoimmune responses involving other tissues, including salivary gland, lacrimal gland, thyroid gland, parathyroid gland, adrenal gland, testis, large bowel, and red blood cells. NOD mice also are susceptible to exogenously induced autoimmune diseases, such as experimental autoimmune thyroiditis, colitis-like wasting disease, encephalomyelitis, and SLE. Defects related to several genes, including the MHC class II, CTLA-4, and IL-2, have been associated with the susceptibility to diabetes. T cells play an important role in the development and progression of disease, whereas B cells are not required at the effector stage of TID in NOD mice.

**Autoimmune Thyroiditis (Experimental Autoimmune Thyroiditis)**

Experimental autoimmune thyroiditis is induced in mice by immunization with murine thyroglobulin plus complete Freund’s adjuvant. The mice develop autoantibodies against thyroglobulin and histological changes consistent with those seen in human autoimmune thyroiditis. It is a useful model for studying the pathogenesis of human chronic (Hashimoto’s) thyroiditis.

**PATHOGENESIS OF AUTOIMMUNE DISEASE**

**Genetic Predisposition**

Genetic, environmental, and random (stochastic) factors all play a role in the pathogenesis of autoimmune diseases. Family members of affected individuals are at higher risk for developing autoimmune disease than the general population. The relative risk to siblings of affected individuals (probands) versus the risk in the general population ($\lambda_s = \frac{\text{disease prevalence in siblings of affected individuals}}{\text{disease prevalence in the general population}}$) is a useful way to estimate the importance of genetic factors. The relative risk is between five- and fiftyfold higher in siblings of affected probands than in unrelated individuals in most autoimmune diseases (Table 6.3). Part of this effect is accounted for by MHC-linked genes.

Twin studies illustrate the importance of these genetic factors. If the concordance rates in monozygotic and dizygotic twins are about the same, the genetic effect is small. For most autoimmune diseases, concordance rates are 15–30 percent for monozygotic twins versus 2–5 percent for...
 dizygotic twins, consistent with a sizeable genetic effect (Table 6.3). Identification of the actual mutations or genetic polymorphisms that confer susceptibility to autoimmune diseases has been complicated by the fact that most autoimmune disorders appear to involve multiple genes, each with only a small effect. Moreover, many autoimmune “diseases” are actually “syndromes” that may arise through a variety of different pathogenic mechanisms and genetic abnormalities. Even in the inbred lupus-prone mouse strain NZB/W, ten or more susceptibility loci are thought to contribute to disease severity in an additive fashion (threshold liability model). Human SLE and other autoimmune diseases also are likely to be highly complex genetically. Interestingly, there may be some overlap genetically between different forms of autoimmune disease, such as SLE and type I diabetes. More than half of the linkages identified in genomewide scanning studies of a variety of systemic and organ-specific autoimmune diseases map nonrandomly into eighteen chromosomal clusters, possibly explaining the occurrence of several autoimmune disease in a given individual or family. For example, Hashimoto’s thyroiditis is associated with a variety of organ-specific (e.g., type I diabetes, pernicious anemia, autoimmune hepatitis, and Addison’s disease) and systemic (e.g., lupus, rheumatoid arthritis, and Sjögren’s syndrome) autoimmune diseases. Pedigrees with more than one systemic autoimmune disorder are not unusual. Of course, shared environmental influences could also explain familial clustering.

Among candidate genes, the MHC class II molecule is the most comprehensively studied. MHC polymorphisms are associated with development of RA, SLE, MS, type I diabetes, and other autoimmune diseases (Table 6.3). Rheumatoid arthritis is a

<table>
<thead>
<tr>
<th>Disease</th>
<th>Concordance Rates</th>
<th>Sibling Risk/Population Risk (λs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dizygotic Twins</td>
<td>Monozygotic Twins</td>
</tr>
<tr>
<td><strong>Systemic autoimmune diseases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>4%</td>
<td>12−15%</td>
</tr>
<tr>
<td>SLE</td>
<td>2%</td>
<td>24%</td>
</tr>
<tr>
<td><strong>Organ specific autoimmune diseases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>5%</td>
<td>33%</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>3.5%</td>
<td>21−40%</td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>0%</td>
<td>36%</td>
</tr>
</tbody>
</table>

striking example. A shared epitope, consisting of a 5-amino acid sequence motif in the third allelic hypervariable region of the HLA-DRβ1 chain (QKRAA in the *0401 allele, QRRAA in the *0404 and *0101 alleles), is carried by 90 percent of patients with RA and is associated with disease severity. In addition to MHC-linked genes, mutations or genetic polymorphisms involving non-MHC genes also are strong candidates for autoimmune disease susceptibility genes (Table 6.4). These include genetic polymorphisms or deficiency of molecules involved in the response to or clearance of immune complexes (e.g., C1q, C4, FcγRIIa, FcγRIIb, FcγRIIIa, mannose binding lectin), which are associated with SLE, as well as genes influencing T-cell activation (PTPN22, CTLA-4), cytokine responses (STAT-4, IRF-5, Tyk2), or programmed cell death (Fas, PDCD1; Table 6.4).

Many, if not most, systemic and organ-specific autoimmune diseases are thought to be multifactorial, involving multiple genetic defects consistent with the threshold liability model of multifactorial inheritance. This model supposes a continuously distributed genetically determined liability to the development of disease. Individuals who develop disease will bear multiple disease susceptibility genes. Because of the normal distribution of genes, first-degree relatives will have much higher risk of developing disease than the general population, second-degree relatives will have a moderate risk, and third-degree relatives will have low risk.

**Environmental Triggers of Autoimmune Disease**

Environmental factors can trigger autoimmune disease in susceptible hosts, as illustrated by the initiation of disease by sun exposure in a subset of lupus patients. The wavelengths most likely to induce lupus fall in the UV range: UVC (200–290 nm), UVB (290–320 nm), and UVA (320–400 nm). UVB irradiation is mostly absorbed in the upper layers of the epidermis, whereas the longer wavelength UVA is able to reach the dermis. UV exposure can induce apoptosis and release of immune mediators and activation of resident dendritic cells and T cells. Expression of certain self-antigens, such as Ro60/Ro52, on the surface of the apoptotic cells may lead to antibody-mediated inflammatory responses that could play a role in the pathogenesis of skin rashes in lupus.

The importance of environmental factors is further illustrated by the induction of a murine lupus syndrome by the hydrocarbon pristane (see “Animal Models of Autoimmune Disease”), which appears to act, in part, through the induction of type I interferon (IFN-α and IFN-β) production. Many other chemicals and drugs have been implicated as triggers of autoimmunity or autoimmune disease. Procainamide, hydralazine, chlorpromazine, methyldopa, quinidine, minocycline, and nitrofurantoin all have been associated with the induction of antinuclear antibodies and in cases antineutrophil cytoplasmic antibodies (ANCA) as well as in the pathogenesis of “drug-induced lupus,” most frequently manifested by serositis (inflammation of the pleura or pericardium) and arthritis. Silica is recognized as a precipitating factor for scleroderma, cigarette smoke may aggravate rheumatoid arthritis, and trichloroethylene is thought to promote lupus in animal models and possibly humans. Other chemical agents implicated in the pathogenesis of autoimmunity include heavy metals such as mercury, gold, and cadmium, pesticides, herbicides, hydrazine, and certain dyes.
Infections also are implicated in the pathogenesis of autoimmune disease. The classic example is rheumatic fever, which is thought to be a consequence of cross-reactivity or “molecular mimicry” between antigens carried by certain strains of streptococci and self-antigens of the heart. Mycoplasma pneumonia can induce the production of cold agglutinins, polyclonal cold-reactive IgM autoantibodies against the erythrocyte I, or i antigens that can cause complement-mediated autoimmune hemolytic anemia (see type II autoimmunity). A variety of other parasitic (e.g., schistosomiasis, Chagas’ disease), bacterial (e.g., Helicobacter pylori, staphylococci, salmonella, Lyme borreliosis), mycobacterial (e.g., tuberculosis, leprosy), and viral (e.g., cytomegalovirus, Epstein-Barr virus, hepatitis C, Coxsackie virus, parvovirus B19) infections can be complicated by autoimmunity. Proposed mechanisms include molecular mimicry and the chronic overproduction of cytokines, such as FN-α. Indeed, therapy with IFN-α can lead to the development of autoimmune diseases such as autoimmune thyroiditis and SLE.

Table 6.4 Some Candidate Non-MHC Autoimmune Disease Susceptibility Genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Abnormality</th>
<th>Disease Association</th>
<th>Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4</td>
<td>Deficiency</td>
<td>SLE</td>
<td>IC clearance</td>
</tr>
<tr>
<td>FcyRIIa</td>
<td>R131</td>
<td>SLE</td>
<td>Inflammatory response to ICs</td>
</tr>
<tr>
<td>FcyRIIb</td>
<td>T232</td>
<td>SLE</td>
<td>Inflammatory response to ICs</td>
</tr>
<tr>
<td>FcyRIIla</td>
<td>F176</td>
<td>SLE</td>
<td>Inflammatory response to ICs</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>+49G</td>
<td>SLE, TID, Graves’ disease, Hashimoto’s thyroiditis, Addison’s disease, celiac disease</td>
<td>Control of T-cell activation</td>
</tr>
<tr>
<td>PTPN22</td>
<td>W620</td>
<td>SLE, RA, type I diabetes, RA, JRA, Graves’ disease, vitiligo</td>
<td>Control of T-cell activation</td>
</tr>
<tr>
<td>STAT4</td>
<td>SNP rs7574865</td>
<td>SLE, RA, type I diabetes, autoimmune thyroiditis, myasthenia gravis</td>
<td>Cytokine signaling</td>
</tr>
<tr>
<td>IRF-5</td>
<td>SNP rs2004640</td>
<td>SLE</td>
<td>Cytokine signaling</td>
</tr>
<tr>
<td>Tyk2</td>
<td>SNP rs2304256</td>
<td>SLE</td>
<td>Cytokine signaling</td>
</tr>
<tr>
<td>PDCD1</td>
<td>SNP rs11568821 (PD-1.3)</td>
<td>SLE</td>
<td>Programmed cell death</td>
</tr>
<tr>
<td>Fas</td>
<td>Deficiency</td>
<td>Autoimmune cytopenias</td>
<td>Programmed cell death</td>
</tr>
<tr>
<td>Foxp3</td>
<td>Deficiency</td>
<td>Organ-specific autoimmune disease (type I diabetes, autoimmune thyroiditis)</td>
<td>Control of T-cell activation (deficiency of T_{reg})</td>
</tr>
</tbody>
</table>

IC, immune complex; JRA, juvenile rheumatoid arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TID, type I diabetes.
Maintenance of Self-Tolerance

Environmental triggers, such as sunlight, drugs/chemicals, and infectious agents, act on a genetic background that regulates tolerance to self. The immune system has evolved a remarkable ability to distinguish self from nonself. Immune tolerance is achieved by multiple mechanisms, operating both centrally and peripherally. Central tolerance occurs during the development of T and B lymphocytes in the thymus and bone marrow, respectively. This mostly involves the deletion of autoreactive cells before they exit the primary lymphoid organs. In general, lymphocytes exhibiting strong reactivity for ubiquitously expressed self-antigens are deleted in this manner, whereas autoreactive cells of lower affinity for self may escape central tolerance. These cells are held in check by peripheral tolerance mechanisms. Peripheral tolerance is mediated by deletion, anergy, and suppression as well as by "neglect" or "ignorance," acting on autoreactive lymphocytes after they exit the primary organs. In general, lymphocyte activation requires two signals, one delivered by the antigen receptor (T-cell antigen receptor or surface immunoglobulin) and second, a "co-stimulatory" signal. For T-cell activation, this co-stimulatory signal is delivered by the interaction of molecules expressed on the surface of professional antigen-presenting cells or B cells, such as CD80 and CD86, which interact with CD28 (or other receptors) on the T-cell surface. In the case of B cells, the co-stimulatory signal is delivered by CD40 ligand, a surface protein expressed by activated helper T cells that interacts with CD40 on the surface of B lymphocytes. In the absence of a co-stimulatory signal, engagement of the T- or B-cell antigen receptor leads to a state of anergy (the inability of the lymphocyte to respond to its specific antigen).

Many self-antigens are expressed at a very low level that is insufficient to induce T-cell activation. In the case of T cells, which recognize short peptides associated with MHC molecules, the induction of self-tolerance requires the generation of a sufficient amount of self-peptide in antigen-presenting cells to stimulate T-cell deletion or anergy. Self-peptides that are generated inefficiently by the antigen-presenting cells can neither stimulate immunity nor induce tolerance; that is, the immune system remains “ignorant” of them. If these minor self-peptides are produced in larger amounts and exposed to the immune system in the presence of an inducer of co-stimulatory molecules (e.g., adjuvants), they have the capacity to stimulate an immune response. This has been shown experimentally with peptides generated in vitro using proteolytic enzymes or using synthetic self-peptides.

Regulatory T cells (T_reg) also play an important role in maintaining peripheral tolerance. Several different subsets of T_reg have been reported, but one of the most intensely studied is the CD4+CD25+Foxp3+ subset, which represents about 10 percent of total CD4+ cells. These cells regulate T-cell activation by a cell–cell-contact-dependent mechanism and through the secretion of inhibitory cytokines such as IL-10 and TGFβ. They suppress both naïve and memory T-cell responses and down-regulate the expression of pro-inflammatory cytokines and co-stimulatory molecules on the antigen-presenting cells. These cells are induced in an antigen-specific manner, but the subsequent suppressive effects are not antigen specific. Genetic defects in Foxp3, a transcription factor that is the key controller of
T_{reg} function, lead to organ-specific autoimmune or autoinflammatory diseases. The scurfy mouse has an X-linked defect of the Foxp3 gene that is lethal in males, which exhibit hyperactivation of CD4\(^{+}\) T cells and overproduction of inflammatory cytokines. Foxp3 mutations in humans are the cause of the IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome) syndrome in humans. These individuals develop organ-specific autoimmune diseases, such as type I diabetes, autoimmune thyroiditis, and inflammatory bowel disease. Interestingly, however, the development of systemic autoimmune disease is not part of the syndrome in either mice or humans.

Finally, antigen-presenting cells play an important role in the induction of tolerance. Dendritic cells can either initiate T-cell activation and proliferation or promote peripheral tolerance through the deletion of autoreactive T cells, depending on their maturation state. Tolerance is induced when antigens are presented by immature dendritic cells and these cells also play a role in the generation and maintenance of T_{reg}.

**TREATMENT OF AUTOIMMUNE DISEASE**

Treatment for autoimmune disease is diverse, and in recent years, the options have increased rapidly. Organ-specific autoimmune diseases of endocrine function, such as type I diabetes and autoimmune thyroiditis, may be treated with hormone replacement. In contrast, other forms of organ-specific autoimmune disease such as autoimmune thrombocytopenia, autoimmune hemolytic anemia, and multiple sclerosis are treated with immunosuppressive medications, as are the majority of systemic autoimmune diseases. Immunosuppressive medications can be categorized by mode of action.

**Anti-inflammatory Agents**

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been used since the 1800s when salicin was extracted from willow bark (1828) and sodium salicylate (1875) and aspirin (1899) were synthesized. A large number of these drugs, which either selectively or nonselectively inhibit the enzyme cyclooxygenase (COX, a synthetic enzyme for prostaglandins), are currently in use to treat inflammatory disease. Although most of their anti-inflammatory properties derive from the inhibition of prostaglandin synthesis, at high doses, there is inhibition of the transcription factor NF\(\kappa\)B, a key mediator of inflammatory cytokine production. Corticosteroids have a more potent effect on NF\(\kappa\)B and consequently a greater anti-inflammatory effect.

Philip S. Hench discovered the anti-inflammatory properties of cortisone in 1949. Corticosteroids are a mainstay of therapy for many systemic autoimmune diseases, including SLE, rheumatoid arthritis, and inflammatory myopathies such as polymyositis. Corticosteroid therapy also is used for the treatment of some of the more serious organ-specific autoimmune diseases, such as autoimmune hemolytic anemia, autoimmune thrombocytopenia, multiple sclerosis, and Goodpasture’s syndrome. Corticosteroids reduce inflammation by multiple mechanisms of action. One major action is enhanced transcription of an inhibitor of NF\(\kappa\)B called I\(\kappa\)B. I\(\kappa\)B dimerizes with NF\(\kappa\)B, inhibiting the production of inflammatory cytokines.
mediated by this transcriptional pathway. In addition, corticosteroids promote the differentiation of a subset of anti-inflammatory macrophages that produce the cytokine IL-10.

**Antimalarial Drugs**

Antimalarial drugs have been used for the treatment of SLE and RA since the early 1900s. The precise mechanism of action remains uncertain, but they have been shown to inhibit cytokine (IL-1 and IL-6) production in vitro. The antimalarials pass freely through cell membranes at neutral pH, but in acidic environments, such as endosomes, they become protonated and can no longer diffuse freely. This leads to concentration of the drug within endosomes and the collapse of endosomal pH gradients. It has been proposed that the inhibition of endosomal acidification interferes with antigen processing or, alternatively, that there is an effect on the interaction of microbial substances such as unmethylated CpG DNA or uridine-rich RNA with endosomal toll-like receptors (TLR9 and TLR7/TLR8, respectively). In addition to SLE and RA, antimalarials are used in the treatment of juvenile rheumatoid arthritis, Sjögren’s syndrome, and inflammatory myopathies.

**Anticytokine Agents**

The development of TNF-α inhibitors in the 1990s ushered in a new era of therapy of autoimmune disease using “biologicals” capable of interfering with the interactions between cytokines and their receptors. The initial clinical use of TNF inhibitors such as etanercept (a soluble recombinant TNF receptor II linked to the Fc portion of human IgG1), infliximab (a chimeric human-mouse anti-TNF-α monoclonal antibody), and adalimumab (a fully humanized monoclonal antibody against TNF-α) in RA demonstrated that although multiple cytokines may be involved in disease pathogenesis (in RA, IL-1, and IL-6 in addition to TNF-α), inhibitors of a single cytokine pathway may show therapeutic efficacy. In addition to RA, TNF-α inhibitors are used for treating inflammatory bowel disease, psoriasis, and psoriatic arthritis and are being tested in sarcoidosis, Wegener’s granulomatosis, pyoderma gangrenosum, SLE, and Behcet’s syndrome.

Anti-TNF therapy is only the tip of the “biological iceberg.” Recombinant IL-1 receptor antagonist (anakinra) has been approved for the treatment of RA, and numerous other cytokine antagonists are currently in clinical trials or under development.

**Methotrexate**

Methotrexate is a folic acid analog used extensively for the treatment of RA. It appears that its ability to inhibit dihydrofolate reductase is not responsible for its efficacy in RA, however. Instead, activity may be related to effects on aminomimidazole-carboxamide-ribotide-transformylase, leading to the release of adenosine, a potent anti-inflammatory molecule that inhibits neutrophil adherence to fibroblasts and endothelial cells. Methotrexate inhibits IL-1 and increases the expression of TH2 cytokines (e.g., IL-4), leading to decreased production of TH1 cytokines (e.g., interferon γ).

**Anti-T-Lymphocyte Therapy**

T cells play a key role in the pathogenesis of type IV autoimmune reactions and
also are critical for generating the T-cell-dependent autoantibodies mediating type II and type III autoimmune diseases. Consequently, considerable effort has gone into the development of therapeutic agents that selectively or nonselectively target T lymphocytes. Drugs that target primarily T cells include cyclophosphamide, azathioprine, cyclosporin A, tacrolimus, and the biological CTLA4-Ig. Cyclophosphamide is an alkylating agent that substitutes alkyl radicals into DNA and RNA. The drug is inactive by itself but is converted to an active metabolite responsible for its immunosuppressive effects. It is used for the treatment of lupus nephritis and other life-threatening complications of SLE and other systemic autoimmune diseases.

Azathioprine is a purine analog that inhibits the synthesis of adenosine and guanine. Like cyclophosphamide, it is converted to an active metabolite (6-mercaptopurine), which inhibits the division of activated B and T cells. Azathioprine is used in the treatment of RA, SLE, autoimmune hepatitis, inflammatory myopathy, vasculitis, and other autoimmune disorders.

Unlike cyclophosphamide and azathioprine, cyclosporine and tacrolimus (FK506) have immunosuppressive that are highly selective for T cells. Both agents interfere with the phosphatase calcineurin, ultimately leading to an inhibition of the activation of the transcription factor NFAT (nuclear factor of activated T cells). Cyclosporine binds to the intracellular protein cyclophilin and tacrolimus to a protein called FK binding protein. The cyclosporine-cyclophilin and tacrolimus-FK binding protein complexes bind to calcineurin, preventing its activation by intracellular calcium, preventing the activation of NFAT. Although used most frequently to prevent transplant rejection, these agents have been shown to have activity in the treatment of RA, SLE, and certain forms of vasculitis.

The CTLA4 (CD152) molecule is an inhibitory receptor expressed by activated T cells that block the co-stimulatory interaction between CD80 or CD86 on the surface of antigen-presenting cells and CD28 on T cells. It acts by binding CD80/CD86 with greater affinity than CD28. CTLA4 is expressed late in T-cell activation and serves to turn off the activated state. CTLA4-Ig (abatacept) is a recombinant chimera of CTLA4 and the Fc fragment of IgG1. CTLA4-Ig/abatacept is used for the treatment of rheumatoid arthritis and is active in mouse models of lupus. Clinical trials in SLE patients are in progress.

**Anti-B-Lymphocyte Therapy**

Rituximab is a cytotoxic chimeric human-mouse monoclonal antibody with a high affinity for CD20, a pan-B-cell surface antigen. It was developed originally for the treatment of B-cell lymphomas. The killing of B cells by rituximab is thought to depend on both the specific recognition of B cells by this monoclonal antibody and natural killer (NK) cell-mediated antibody-dependent cellular cytotoxicity (ADCC) of those cells. There is considerable evidence that the interaction of B-cell-bound monoclonal antibodies with NK cell CD16 (FcyRIIIA) is a critical event leading to ADCC following treatment with rituximab. Rituximab appears to have activity in a variety of autoimmune diseases associated with autoantibody production, including RA, SLE, polymyositis/dermatomyositis, Sjögren’s syndrome, and cryoglobulinemic vasculitis.
**Intravenous Immunoglobulin**

Intravenous immunoglobulin (IVIG) is a preparation of human immunoglobulin pooled from thousands of healthy individuals. It was originally developed for replacement therapy in humoral immunodeficiency syndromes but has more recently become an important therapeutic modality in severe autoimmune disorders, such as thrombocytopenic purpura, autoimmune hemolytic anemia, neuroimmunological diseases such as Guillain-Barré syndrome, SLE, certain forms of vasculitis, and polymyositis/dermatomyositis. The mechanism of action remains unclear, but IVIG may block the function of Fc receptors expressed by phagocytes of the reticuloendothelial system and also induces FcγRIIB (inhibitory Fc receptor) expression on infiltrating macrophages in the K/BxN model of RA. An additional mode of action may involve the presence of anti-idiotypic antibodies that block the antigen combining sites of pathogenic antibodies. The duration of action is limited by the metabolism of serum immunoglobulin, and generally, IVIG is regarded as a temporary measure that is followed by more definitive therapy.

**Autologous Hematopoietic Stem Cell Transplantation**

The ability to adoptively transfer autoimmune diseases with bone marrow transplantation in a variety of animal models provides strong evidence that these disorders are mediated by cells derived from hematopoietic cells. There is compelling evidence that autoimmune disease results from a loss of B- or T-cell tolerance to certain self-antigens. Hematopoietic stem cells are the earliest progenitor cells of the immune system and give rise to B and T lymphocytes as well as antigen-presenting cells (monocytes, macrophages, and dendritic cells). The rationale for HSCT as a therapy for autoimmune disease is based on the concept that the peripheral expansion of autoreactive T- and B-cell clones is central to the pathogenesis of autoimmunity. If these autoantigen-specific cells can be deleted and the immune system regenerated with “normal” hematopoietic stem cells, there is the potential to effect a “cure” of autoimmune disease. Therapy is based on the mobilization of hematopoietic stem cells using C-CSF or G-CSF plus cyclophosphamide. There is the risk during mobilization of flares caused by G-CSF treatment. The stem cells are depleted of lymphocytes and enriched for CD34+ cells followed by expansion and reinfusion into the same donor after “conditioning.” The conditioning regimen involves cyclophosphamide treatment or other immunosuppressive treatments aimed at depleting mature lymphocytes. Phase III clinical trials of the efficacy of autologous HSCT in multiple sclerosis, SLE, RA, and scleroderma are ongoing or planned. Promising preliminary results have been obtained with all of these conditions, but further study is needed.

**THE FUTURE**

**Therapy Directed at Inflammatory Pathways**

The pace of changes in the field of autoimmunity is rapid. Recent advances in understanding the importance of key inflammatory pathways involved in specific diseases, such as the TNF-α pathway in RA, inflammatory bowel disease, and other disorders, have been quickly followed by new biological therapies designed to interfere with these pathways.
With recent data increasingly underscoring the importance of type I interferon pathways in the pathogenesis of lupus, it seems reasonable to expect that therapies directed at preventing the excessive production of IFN-α/-β will be tested in the near future. As always, a major challenge in immune therapy will be to treat the key immunological defects selectively, leaving the remainder of the immune system intact to deal with infections. As the important immunological pathways become better defined, it may be feasible to selectively target one part of the pathway while leaving others intact. For instance, type I interferon is produced through several interrelated pathways. If only one of them is found to be abnormal in SLE, it may be feasible to selectively blockade that pathway, leaving the others intact to deal with viral and other types of infections.

**Gene Therapy**

Although considerable progress has been made in defining the genetics of autoimmune disease, nearly all of the major systemic autoimmune diseases are highly complex, multigene disorders, even in animal models. In comparison with single-gene diseases, such as cystic fibrosis or α1-antitrypsin deficiency, it may prove considerably more difficult to correct genetically complex autoimmune disorders using standard gene therapy approaches. However, there may be reason for cautious optimism because inhibition of a single cytokine (TNF-α) can have a significant beneficial effect in the treatment of a multigene autoimmune disorder (RA). At least in mice, retroviral transduction of Foxp3 has been shown to convert naïve T cells into cells that phenotypically and functionally resemble Treg. Whether this approach will be applicable to the therapy of autoimmune disease remains to be determined.

**Cell Therapy**

Another promising possibility involves manipulating tolerance through the use of suppressor T cells or immature dendritic cells. Decreasing the numbers of CD25⁺CD4⁺Foxp3⁺ cells in mice can induce a variety of organ-specific autoimmune conditions. Conversely, expansion of this subset can be used to induce immune tolerance in transplantation models. There is considerable interest in the potential use of Treg expansion either in vivo or in vitro in the treatment for autoimmune disease. Treg are highly proliferative in vivo, and certain drugs, such as rapamycin, may increase the ratio of Treg to T effector cells. Alternatively, Treg can be expanded in vitro in the presence of high doses of IL-2 and self-antigen followed by reinfusion, an approach that has been used successfully in the treatment of type I diabetes in NOD mice.

Whereas mature dendritic cells are highly potent stimulatory antigen-presenting cells, immature dendritic cells are tolerogenic. Dendritic cell therapy is being explored as a means of both promoting immunity (mature DCs) and inducing tolerance (immature DCs). Immune silencing may be made feasible by loading DCs ex vivo with self-antigens followed by treatments that render them tolerogenic (TGFβ, retinoic acid, or rapamycin, for instance). Reinfusion of these cells may be useful for inducing tolerance, though numerous obstacles remain.

**Stem Cell Therapy**

Although the bulk of evidence suggests that autoimmune diseases arises primarily
due to defects in the immune system, therapy directed at repairing the target organs also may be equally important. Thus, there is increasing interest in the possibility of repairing damage at the level of the target organs stem cell therapy.

MESENCHYMAL STEM CELLS

Found in bone marrow, cord blood, spleen, adipose tissue, and other tissues, mesenchymal stem cells (MSCs) are a well-characterized population of adult stem cells that can give rise to three main cell types, including adipocytes, chondrocytes, and osteoblasts. However, these cells may be induced experimentally to undergo differentiation into other cell types as well, such as neural cells and myogenic cells. Isolation, amplification, and large-scale in vitro culturing of MSCs has been mastered to a degree appropriate for clinical applications, making MSCs good candidates for use in tissue repair. These cells can be maintained and propagated in culture for long periods, without losing their capacity to form the cell types discussed earlier. Another advantage is that MSCs can take up and retain introduced genes, a property that can be exploited for the delivery of clinically beneficial proteins to targeted locations. MSCs are also amenable to cryopreservation, allowing their future use in “off-the-shelf” therapies. Animal studies seeking to reconstitute or repair damaged cartilage, bone, muscle, heart muscle, and tendon using MSCs have shown great promise, raising the possibility that they might one day be used for repairing tissues damaged by autoimmune attack. Indeed, cell therapy using MSCs can prevent damage to the joints in collagen-induced arthritis and also can ameliorate end-organ damage in EAE and murine lupus.

Interestingly, allogeneic bone marrow–derived MSCs or stromal cells (BMSCs) suppress in vitro T- and B-cell proliferation in a non-MHC-dependent manner. The immunosuppressive activity of MSCs has been attributed to effects on the expansion of the CD25+CD4+Foxp3+ T_{reg} population.

Current tissue engineering strategies tend to rely on the use autologous sources of adult stem cells. However, data demonstrating that the transplantation of allogeneic adult mesenchymal stem cells is feasible has the potential to revolutionize this field. With routine access to adult stem cells at the point of care, physicians may be able to incorporate tissue-engineering approaches into the management of autoimmune disease.

HUMAN EMBRYONIC STEM CELLS

Very recent advances in stem cell technology enable the generation of pluripotent human stem cells from human somatic cells using a process known as reprogramming or dedifferentiation. The procedure exploits viral vector-mediated expression of only four genes (namely, c-myc, oct3/4, sox2, and klf4) to reprogram mouse and human somatic cells (specifically, skin fibroblasts) into embryonic-like “induced pluripotent stem cells” (iPS cells). These cells appear to be just as plastic as embryonic stem cells, but one drawback to their clinical application in humans is the use of lentiviral or other retroviral vectors to introduce the genes. Although still at an early stage, the use of iPS cells could greatly advance the practicality of regenerative medicine as a therapeutic option. By creating patient-specific, pluripotent human stem cells, cell replacement therapies that avoid human embryo destruction may now be within reach.
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BIBLIOGRAPHY

REVIEWS


SUGGESTED READING


