CHAPTER

52

Plasma Proteins & Immunoglobulins

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BIOMEDICAL IMPORTANCE

The proteins that circulate in blood plasma play important roles in human physiology. **Albumins** facilitate the transit of fatty acids, steroid hormones, and other ligands between tissues, while **transferrin** aids the uptake and distribution of iron. Circulating **fibrinogen** serves as a readily mobilized building block of the fibrin mesh that provides the foundation of the clots used to seal injured vessels. Formation of these clots is triggered by a cascade of latent proteases, or **zymogens**, called blood coagulation factors. Plasma also contains several proteins that function as inhibitors of proteolytic enzymes. **Antithrombin** helps confine the formation of clots to the vicinity of a wound, while α_1-antiproteinase and α_2-macroglobulin shield healthy tissues from the proteases that destroy invading pathogens and remove dead or defective cells. Circulating immunoglobulins called **antibodies** form the front line of the body's immune system.

Perturbances in the production of plasma proteins can have serious health consequences. Deficiencies in key components of the blood clotting cascade can result in excessive bruising and bleeding (**hemophilia**). Persons lacking plasma ceruloplasmin, the body's primary carrier of copper, are subject to hepatolenticular degeneration (Wilson disease), while emphysema is associated with a genetic deficiency in the production of circulating α_1-antiproteinase. More than one in every 30 residents of North America suffer from an **autoimmune disorder**, such as type 1 diabetes, asthma, and rheumatoid arthritis, resulting from the production of aberrant immunoglobulins (**Table 52–1**). Insufficiencies in the production of protective antibodies, such as occur in many persons infected by the **human immunodeficiency virus** (HIV) or patients administered immunosuppressant drugs, render them immunocompromised, extremely susceptible to infection by microbial and viral pathogens. While the root causes of plasma protein–related diseases such as hemophilia are relatively straightforward, others—in particular many autoimmune disorders—arise due to the complex and cryptic interplay of genetic, dietary, nutritional, environmental, and medical factors.

THE BLOOD HAS MANY FUNCTIONS

As the primary avenue by which tissues are connected to each other and the surrounding environment, the blood that circulates throughout our body performs a variety of functions. These include delivering nutrients

and oxygen, removing waste products, conveying hormones, and defending against infectious microorganisms (**Table 52–2**). These myriad functions are carried out by a diverse set of components that include cellular entities such as red blood cells, platelets, and leukocytes (see Chapters 53 and 54), and the water, electrolytes, metabolites, nutrients, proteins, and hormones that comprise the **plasma**.

TABLE 52–2 Major Functions of Blood

1. **Respiration**—transport of oxygen from the lungs to the tissues and of CO_2 from the tissues to the lungs
2. **Nutrition**—transport of absorbed food materials
3. **Excretion**—transport of metabolic waste to the kidneys, lungs, skin, and intestines for removal
4. Maintenance of the normal **acid–base balance** in the body
5. Regulation of **water balance** through the effects of blood on the exchange of water between the circulating fluid and the tissue fluid
6. Regulation of **body temperature** by the distribution of body heat
7. **Defense** against infection by the white blood cells and circulating antibodies
8. Transport of **hormones** and regulation of metabolism
9. Transport of **metabolites**
10. **Coagulation**

PLASMA CONTAINS A COMPLEX MIXTURE OF PROTEINS

Plasma contains a complex mixture of proteins. Early scientists classified these proteins into three groups, **fibrinogen**, **albumin**, and **globulins**, on the basis of their relative solubility in the presence of added organic solvents such as ethanol or salting out agents such as as ammonium sulfate. Subsequently, clinical scientists employed electrophoresis within a **cellulose acetate** matrix to analyze the protein composition of plasma. Using this technique, salt-soluble serum protein fraction separated into five major components designated albumin and the α_1-, α_2-, β-, and γ-**globulins**, respectively (**Figure 52–1**). Plasma proteins tend to be rich in disulfide bonds and frequently contain bound carbohydrate

(**glycoproteins**) or lipid (**lipoproteins**). The relative dimensions and molecular masses of several plasma proteins are shown in **Figure 52–2**.

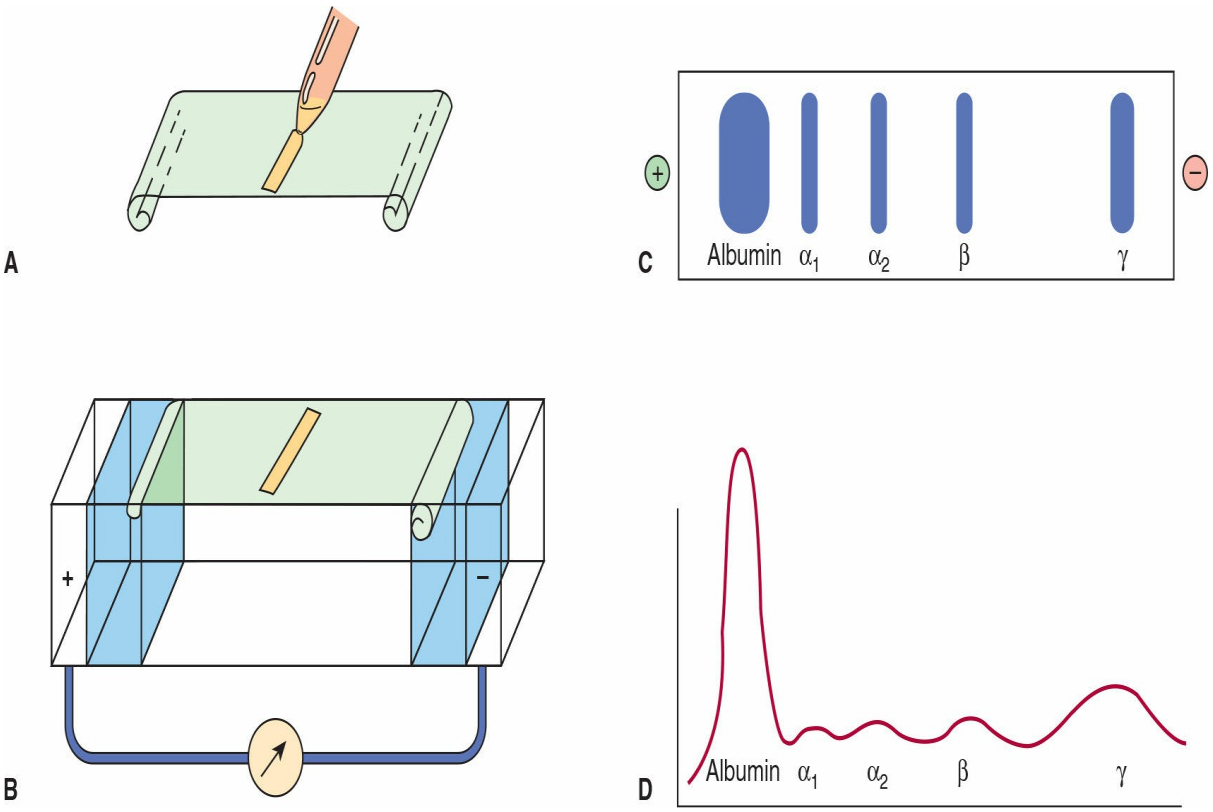

FIGURE 52–1 Technique of cellulose acetate zone electrophoresis. (A) A small amount of serum or other fluid is applied to a cellulose acetate strip. **(B)** Electrophoresis in electrolyte buffer is performed. **(C)** Staining enables separated bands of protein to be visualized. **(D)** Densitometer scanning reveals the relative mobilities of albumin, α_1-globulin, β_2-globulin, β-globulin, and γ-globulin. (Reproduced, with permission, from Parslow TG et al (editors): *Medical Immunology*, 10th ed. McGraw-Hill, 2001.)

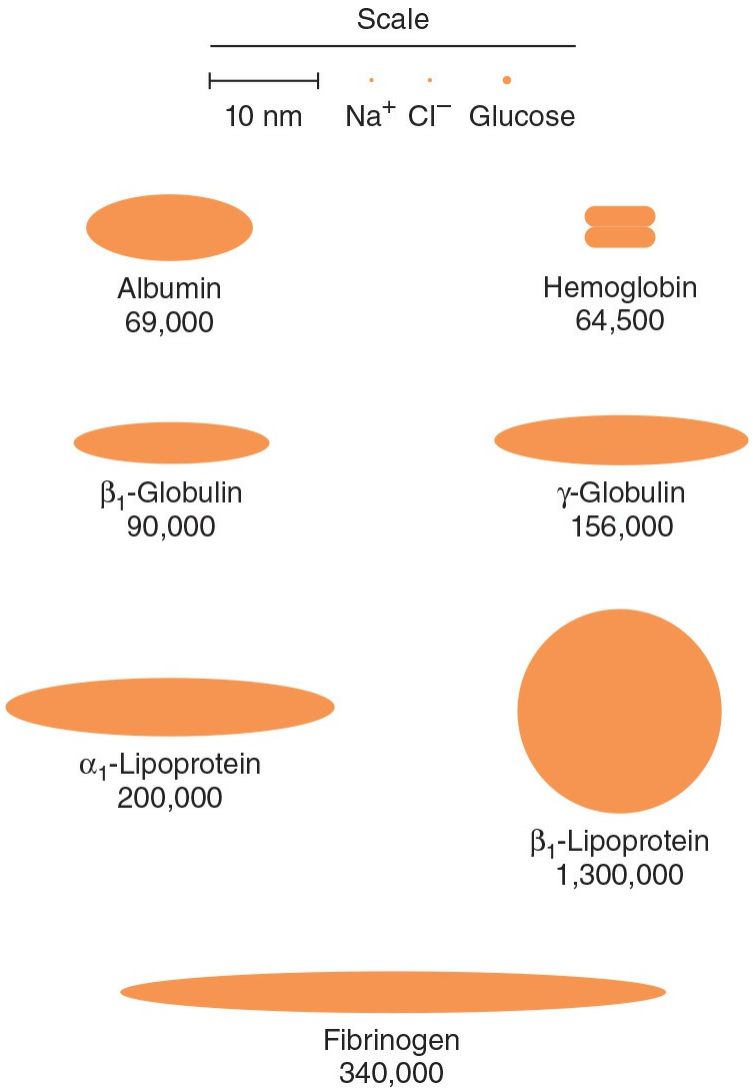

FIGURE 52–2 Relative dimensions and approximate molecular masses of protein molecules in the blood.

Plasma Proteins Help Determine the Distribution of Fluid Between Blood & Tissues

The aggregate concentration of the proteins present in human plasma typically falls in the range of 7 to 7.5 g/dL. The resulting **osmotic pressure** (oncotic pressure) is approximately 25 mm Hg. Since the **hydrostatic pressure** in the arterioles is approximately 37 mm Hg, with an interstitial (tissue) pressure of 1 mm Hg opposing it, a net outward force of about 11 mm Hg drives fluid from the plasma into the interstitial spaces. By contrast, the hydrostatic pressure in venules is about 17 mm Hg; thus, a net force of about 9 mm Hg drives water from tissues back into the circulation. The above pressures are often referred to as the **Starling forces**. If the concentration of plasma proteins is markedly diminished (eg,

due to severe protein malnutrition), fluid will cease flowing back into the intravascular compartment and begin to accumulate in the extravascular tissue spaces, resulting in a condition known as **edema**.

Most Plasma Proteins Are Synthesized in the Liver

Roughly 70 to 80% of all plasma proteins are synthesized in the liver. These include albumin, fibrinogen, transferrin, and most components of the complement and blood coagulation cascades. Two prominent exceptions are von Willebrand factor, which is synthesized in the vascular endothelium, and the γ-globulins, which are synthesized in the lymphocytes. Most plasma proteins are covalently modified by the addition of either N- or O-linked oligosaccharide chains, or both (see Chapter 46). Albumin is the major exception. These oligosaccharide chains fulfill a variety of functions (see Table 46–2). Loss of terminal sialic acid residues accelerates clearance of plasma glycoproteins from the circulation.

As is the case for other proteins destined for secretion from a cell, the genes for plasma proteins code for an amino-terminal **signal sequence** that targets them to the endoplasmic reticulum. As this leader sequence emerges from the ribosome, it binds to a transmembrane protein complex in the endoplasmic reticulum called the **signal recognition particle**. The emerging polypeptide chain is pulled through the signal recognition particle into the lumen of the endoplasmic reticulum, during which process the leader sequence is cleaved off by an associated **signal peptidase** (see Chapter 49). The newly synthesized proteins then traverse the major secretory route in the cell (rough endoplasmic membrane → smooth endoplasmic membrane → Golgi apparatus → secretory vesicles) prior to entering the plasma, during which process they are subject to various posttranslational modifications (proteolysis, glycosylation, phosphorylation, etc). Transit times from the site of synthesis in the hepatocyte from to the plasma vary from 30 minutes to several hours for individual proteins.

Many Plasma Proteins Exhibit Polymorphism

A **polymorphism** is a mendelian or monogenic trait that exists in the population in at least two phenotypes, neither of which is rare (ie, it occurs with frequency of at least 1-2%). Most polymorphisms are innocuous. The ABO blood group substances (see Chapter 53) are perhaps the best known

example of a human polymorphism. Other human plasma proteins that exhibit polymorphism include α_1-antitrypsin, haptoglobin, transferrin, ceruloplasmin, and immunoglobulins.

Each Plasma Protein Has a Characteristic Half-Life in the Circulation

The **half-life** of a plasma protein is the time required for 50% of the molecules present at any given moment to be degraded or otherwise cleared from the blood. For example, the half-lives of albumin and haptoglobin in healthy adults are approximately 20 and 5 days, respectively. Under normal circumstances, as older protein molecules are cleared they are replaced by newly synthesized ones, a process called **turnover**. During normal turnover, the total concentration of these proteins will remain constant as the countervailing processes of synthesis and clearance reach a **steady state**.

In certain diseases, the half-life of a protein may be markedly altered. For instance, in some gastrointestinal diseases such as regional ileitis (Crohn disease), considerable amounts of plasma proteins, including albumin, may be lost into the bowel through the inflamed intestinal mucosa. The half-life of albumin in these subjects may be reduced to as little as 1 day, a condition referred to as a **protein-losing gastroenteropathy**.

ALBUMIN IS THE MOST ABUNDANT PROTEIN IN HUMAN PLASMA

The liver synthesizes approximately 12 g of albumin per day, representing about 25% of total hepatic protein synthesis and half its secreted protein. About 40% of the body's albumin circulates in the plasma, where it accounts for roughly three-fifths of total plasma protein by weight (3.4-4.7 g/dL). The remainder resides in the extracellular space. Because of its relatively low molecular mass (about 69 kDa) and high concentration, albumin is thought to contribute 75 to 80% of the **osmotic pressure** of human plasma. Like most other secreted proteins, albumin is initially synthesized as a **preproprotein**. Its **signal peptide** is removed as it passes into the cisternae of the rough endoplasmic reticulum. A second **hexapeptide** is cleaved from the new N-terminus farther along the secretory pathway.

Mature human albumin consists of a single polypeptide chain, 585 amino acids in length, that is organized into three functional domains. Its ellipsoidal conformation is stabilized by a total of 17 intrachain disulfide bonds. A major role of albumin is to bind to and transport numerous **ligands**. These include free fatty acids (FFA), calcium, certain steroid hormones, bilirubin, copper, and tryptophan. A variety of drugs, including sulfonamides, penicillin G, dicumarol, and aspirin, also bind to albumin; a finding with important pharmacologic implications. Preparations of human albumin have been widely used in the treatment of burns and of hemorrhagic shock.

Some humans suffer from genetic mutations that impair their ability to synthesize albumin. Individuals whose plasma is completely devoid of albumin are said to exhibit **analbuminemia**. Surprisingly, persons suffering from analbuminemia display only moderate edema. Depressed synthesis of albumin also occurs in a variety of diseases, particularly those of the liver. The plasma of patients with **liver disease** often shows a decrease in the ratio of albumin to globulins (decreased albumin-globulin ratio). The synthesis of albumin decreases relatively early in conditions of protein malnutrition, such as **kwashiorkor**.

THE LEVELS OF CERTAIN PLASMA PROTEINS INCREASE DURING INFLAMMATION OR FOLLOWING TISSUE DAMAGE

Table 52–3 summarizes the functions of many of the plasma proteins. **C-reactive protein** (CRP, so named because it reacts with the C polysaccharide of pneumococci), α_1-antiproteinase, haptoglobin, α_1-acid glycoprotein, and fibrinogen are classified as **acute-phase proteins**. Acute-phase proteins are believed to play a role in the body's response to inflammation. C-reactive protein stimulates the complement pathway (see below), while α_1-antitrypsin neutralizes certain proteases released during acute inflammation.

TABLE 52–3 Some Functions of Plasma Proteins

Function	Plasma Proteins
Antiproteases	Antichymotrypsin α_1-Antitrypsin (α_1-antiproteinase) α_2-Macroglobulin Antithrombin
Blood clotting	Various coagulation factors, fibrinogen
Enzymes	Function in blood, for example, coagulation factors, cholinesterase Leakage from cells or tissues, eg, aminotransferases
Hormones	Erythropoietin[a]
Immune defense	Immunoglobulins, complement proteins, and β_2-macroglobulin
Involvement in inflammatory responses	Acute phase response proteins (eg, C-reactive protein, α_1-acid glycoprotein [orosomucoid])
Oncofetal	α_1-Fetoprotein (AFP)
Transport or binding proteins	Albumin (various ligands, including bilirubin, free fatty acids, ions [Ca^{2+}], metals [eg, Cu^{2+}, Zn^{2+}], metheme, steroids, other hormones, and a variety of drugs) Corticosteroid-binding globulin (transcortin) (binds cortisol) Haptoglobin (binds extracorpuscular hemoglobin) Lipoproteins (chylomicrons, VLDL, LDL, HDL) Hemopexin (binds heme) Retinol-binding protein (binds retinol) Sex-hormone-binding globulin (binds testosterone, estradiol) Thyroid-binding globulin (binds T_4, T_3) Transferrin (transport iron) Transthyretin (formerly prealbumin; binds T_4 and forms a complex, with retinol-binding protein)

The levels of acute-phase proteins may increase by 50% to as much as 1000-fold (in the case of CRP) during chronic inflammatory states and in

patients with cancer. I**nterleukin 1 (IL-1)**, a polypeptide released from mononuclear phagocytic cells, is the principal—but not the sole—stimulator of acute-phase reactant synthesis by hepatocytes. Additional molecules such as IL-6 also participate. Because its concentration can rise so dramatically, CRP is used as a biomarker of tissue injury, infection, and inflammation.

The small proteins such as interferons, ILs, and tumor necrosis factors that facilitate cell–cell communication between the components of the immune system are called **cytokines**. Cytokines can be both autocrine and paracrine in nature. One of the primary targets of IL-1 and IL-6 is **nuclear factor kappa-B (NFκB)**, a transcription factor that regulates the expression of the genes encoding many cytokines, chemokines, growth factors, and cell adhesion molecules. NFκB, a heterodimer comprised of a 50- and a 65-kDa polypeptide, normally resides in the cytosol as an inactive complex with a second protein, NFκB inhibitor-α, also known as **IκBα**. When stimulation by inflammation, injury, or radiation, IκBα becomes phosphorylated, which targets it for ubiquitination and degradation. Once freed from its inhibitory partner, active NFκB translocates to the nucleus where it stimulates transcription of its target genes.

HAPTOGLOBIN PROTECTS THE KIDNEYS

Iron in Senescent Erythrocytes Is Recycled by Macrophages

Erythrocytes normally have a lifespan of approximately 120 days. Senescent or damaged erythrocytes are phagocytosed by macrophages of the reticuloendothelial system (RES) present in the spleen and liver. Around 200 billion erythrocytes are catabolized every day. Within the macrophage, heme derived from hemoglobin is converted by the enzym **heme oxygenase** to biliverdin (see Figure 31–13), releasing carbon monoxide and iron as by-products. Iron released from heme is exported from phagocytic vesicles in the macrophage by **NRAMP 1** (natural resistance–associated macrophage protein 1), a transporter homologous to DMT1. Iron is subsequently secreted into the circulation by the transmembrane protein ferroportin (**Figure 52–3**). Thus, ferroportin plays a central role in both iron absorption by the intestine and iron secretion from macrophages.

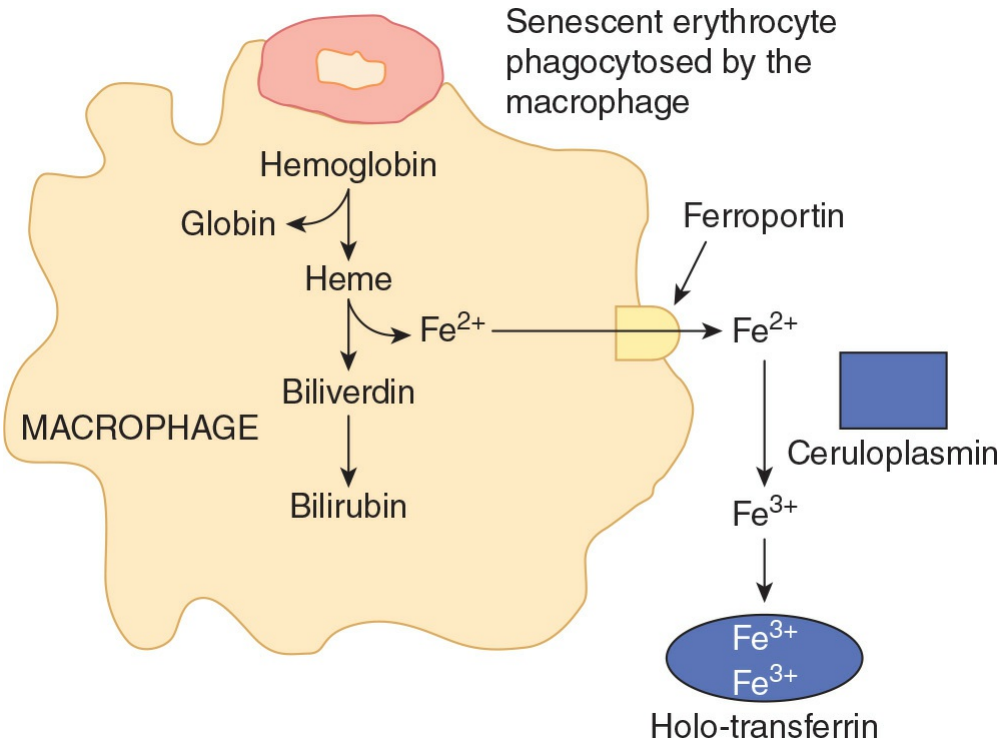

FIGURE 52–3 Recycling of iron in macrophages. Senescent erythrocytes are phagocytosed by macrophages. Hemoglobin is degraded and iron is released from heme by the action of the enzyme heme oxygenase. Ferrous iron is then transported out of the macrophage via ferroportin (Fp). In the plasma, it is oxidized to the ferric form by ceruloplasmin before binding to transferrin (Tf). Iron circulates in blood tightly bound to Tf.

In the blood, Fe^{2+} is oxidized to Fe^{3+} in a reaction catalyzed by the ferrioxidase **ceruloplasmin** (see below), a copper-containing plasma enzyme synthesized by liver. Once oxidized, Fe^{3+} is then bound to transferrin in blood. The iron released from macrophages in this way (about 25 mg/d) is recycled, thereby reducing the need for intestinal iron absorption, which averages only 1 to 2 mg/d.

Haptoglobin Scavenges Hemoglobin That Has Escaped Recycling

During the course of red blood cell turnover, approximately 10% of an erythrocyte's hemoglobin escapes into the circulation. This free, **extracorpuscular** hemoglobin is sufficiently small at ≈65 kDa to pass through the glomerulus of the kidney into the tubules, where it tends to form damaging precipitates. **Haptoglobin** (Hp) is a plasma glycoprotein

that binds extracorpuscular hemoglobin (Hb), forming a tight noncovalent complex (Hb-Hp). Human haptoglobin exists in **three polymorphic forms**, known as Hp 1-1, Hp 2-1, and Hp 2-2 that reflect the patterns of inheritance of two genes, designated Hp^1 and Hp^2. Homozygotes synthesize Hp 1-1 or Hp 1-2, respectively, while Hp 2-1 is synthesized by heterozygotes.

Normally, the level of haptoglobin in a deciliter of human plasma is sufficient to bind 40 to 180 mg of hemoglobin. Since the resulting Hb-Hp complex is too large (≥ 155 kDa) to pass through the glomerulus, the kidney is protected from the formation of harmful precipitates while the loss of the iron associated with extracorpuscular hemoglobin is reduced.

Certain other plasma proteins **bind heme**, but not hemoglobin. They include a β_1-globulin hemopexin, which binds free heme, and **albumin**, which binds metheme (ferric heme) to form methemalbumin. Methemalbumin subsequently transfers this metheme to hemopexin.

Haptoglobin Can Serve as a Diagnostic Indicator

In situations where hemoglobin is constantly being released from red blood cells, such as occurs in hemolytic anemias, the level of haptoglobin can fall dramatically. This decrease reflects the marked difference in the half-lives of free haptoglobin, approximately 5 days, and the Hb-Hp complex, approximately 90 minutes. The level of **haptoglobin-related protein**, a homologue of haptoglobin also present in plasma, is elevated in some patients with cancers, although the significance of this is not understood.

IRON IS STRICTLY CONSERVED

Iron is a key constituent of many human proteins, including hemoglobin, myoglobin, the cytochrome P450 group of enzymes, numerous components of the electron transport chain, and ribonucleotide reductase, which catalyzes the conversion of ribonucleotides into deoxyribonucleotides. Body iron, which is distributed as shown in **Table 52–4**, is highly conserved. A healthy adult loses only about 1 to 1.5 mg (< 0.05%) of their 3 to 4 g of body iron each day. However, an adult premenopausal female can experience iron deficiency due to blood loss during menstruation.

TABLE 52–4 Distribution of Iron in a 70-kg Adult Male[a]

Transferrin	3-4 mg
Hemoglobin in red blood cells	2500 mg
In myoglobin and various enzymes	300 mg
In stores (ferritin)	1000 mg
Absorption	1 mg/d
Losses	1 mg/d

Oxidation by Ceruloplasmin Is a Key Feature of the Iron Cycle

Macrophages play a key role in the turnover of red blood cells. Following phagocytosis and digestion via lysosomal hydrolases, the iron is expelled largely in the ferrous, Fe^{2+}, state. In order to be recovered via the transferrin cycle, this iron must be oxidized to the ferric, Fe^{3+}, state by the ferroxidase **ceruloplasmin**, a 160-kDa α_2-globulin synthesized by the liver. With six, catalytically essential, copper atoms, ceruloplasmin is the major copper-containing protein in plasma.

Deficiencies in Ceruloplasmin Perturb Iron Homeostasis

Ceruloplasmin deficiency can arise from genetic causes as well as a lack of copper, an essential micronutrient, in the diet. When adequate quantities of catalytically functional ceruloplasmin are lacking, the body's ability to recycle Fe^{2+} becomes impaired, leading to iron accumulation in tissues. While persons suffering from **hypoceruloplasmenia**, a genetically heritable condition in which ceruloplasmin levels are roughly 50% of normal, generally display no clinical abnormalities, genetic mutations that abolish the ferroxidase activity of ceruloplasmin, **aceruloplasminemia**, can have severe physiologic consequences. If left untreated, the progressive accumulation of iron in pancreatic islet cells and basal ganglia eventually leads to the development of insulin-dependent diabetes and neurologic degeneration that may manifest as dementia, dysarthria, and dystonia.

Ceruloplasmin Levels Decrease in Wilson Disease

In **Wilson disease**, a mutation in the gene for a **copper-binding P-type ATPase** (ATP7B protein) blocks the excretion of excess copper in the bile. As a consequence, copper accumulates in the liver, brain, kidney, and red blood cells. Paradoxically, rising levels of copper within the liver apparently interferes with the incorporation of this metal into newly synthesized ceruloplasmin polypeptides (apoceruloplasm) leading to a fall in plasma ceruloplasmin levels. If left untreated, patients suffering from this form of **copper toxicosis** may develop a hemolytic anemia or chronic liver disease (cirrhosis and hepatitis). Accumulation of copper in the basal ganglia and other centers can lead to neurologic symptoms. Wilson disease can be treated by limiting the dietary intake of copper while depleting any excess copper by the regular administration of **penicillamine**, which chelates copper and is subsequently excreted in the urine.

SERUM INHIBITORS PREVENT INDISCRIMINATE PROTEOLYSIS

Proteases are essential participants in tissue remodeling, blood clotting, elimination of old or diseased cells, destruction of invading pathogens, and other physiologic functions. Left unchecked, however, proteolytic enzymes that are secreted or escape into the blood can damage healthy

tissue. Protection from indiscriminate proteolysis involves a battery of serum proteins that inhibit, and thereby limit the scope of, protease action.

Deficiency of α_1-Antiproteinase Is Associated With Emphysema & Liver Disease

α1-Antiproteinase, a 394-residue glycoprotein that makes up >90% of the α_1-albumin fraction, is the principal **serine protease inhibitor (serpin)** in human plasma. Formerly called α_1-antitrypsin, α_1-antiproteinase inhibits trypsin, elastase, and other serine proteases by forming an inactive covalent complex with them. α_1-Antiproteinase is synthesized by hepatocytes and macrophages. At least 75 **polymorphic forms** of this serpin, or Pi, exist. The major genotype is MM, whose phenotypic product is PiM. A deficiency in α_1-antiproteinase plays a role in some cases (~ 5%) of emphysema, particularly in subjects with the **ZZ genotype** (who synthesize PiZ) and in PiSZ heterozygotes, both of whom secrete lower levels of serpins than PiMM individuals.

Oxidation of Met_{358} Inactivates α_1-Antiproteinase

In the lungs, components of the smoke produced by burning tobacco products and industrial activities can oxidize a key **methionine** residue, Met_{358}, located in the protease-binding domain of α_1-antiproteinase. Oxidation renders α_1-antiproteinase unable to covalently bind and neutralize serine proteases. The subsequent damage produced by unchecked proteolytic activity in the lungs can contribute to the development of emphysema. Smoking can be particularly devastating for patients who already have low levels of α_1-antiproteinase (eg, PiZZ phenotype). Intravenous administration of serpins (augmentation therapy) has been used as an adjunct in the treatment of patients with emphysema that exhibit α_1-antiproteinase deficiency.

Individuals deficient in α_1-antiproteinase are also at greater risk of lung damage from pneumonia or other conditions that induce the accumulation of polymorphonuclear white blood cells in the lung. Deficiency of α_1-antiproteinase is also implicated in **α_1-antitrypsin deficiency liver disease**, a form of cirrhosis that afflicts persons possessing the ZZ phenotype. In these individuals, substitution of Glu_{342} by **lysine** promotes

the formation of polymeric aggregates of α_1-antiproteinase in the cisternae of the endoplasmic reticulum in hepatic cells.

α_2-Macroglobulin Neutralizes Proteases & Targets Cytokines to Tissues

α2-Macroglobulin, a member of the thioester plasma protein family, comprises 8 to 10% of the total plasma protein in humans. This homotetrameric glycoprotein is the most abundant member of a group of homologous plasma proteins that include complement proteins C3 and C4. α_2-Macroglobulin is synthesized by monocytes, hepatocytes, and astrocytes. It mediates the inhibition and clearance of a broad spectrum of truant proteases by a "Venus flytrap" mechanism. The key components of the trap include a 35-residue "bait domain" located near the center of its polypeptide sequence and an internal cyclic thioester linking a cysteine and a glutamine residue (**Figure 52–10**). Cleavage of the bait domain produces a massive conformational change, triggering the envelopment of the attacking protease. The reactive thioester then reacts with the protease to covalently link the two proteins. This conformational change also exposes a sequence in α_2-macroglobulin that is recognized by cell surface receptors that subsequently bind and remove the complex from the plasma.

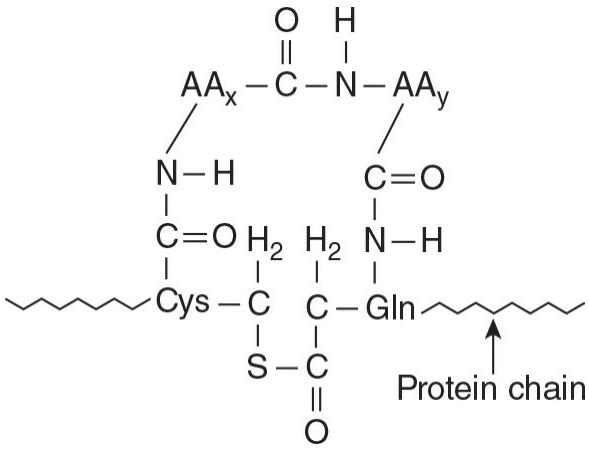

FIGURE 52–10 An internal cyclic thiol ester bond, as present in α_2-macroglobulin. AA_x and AA_y are neighboring amino acids to cysteine and glutamine.

In addition to serving as the plasma's predominant broad-spectrum, or **panproteinase**, inhibitor, α_2-macroglobulin also binds to and transports

approximately 10% of the **zinc** in plasma (the remainder being transported by albumin) as well as **cytokines** such as platelet-derived growth factor and transforming growth factor β. As a cytokine transporter, α_2-macroglobulin appears to be involved in targeting these effectors toward particular tissues or cells. Once taken up by cells, the cytokines dissociate, freeing them to modulate their growth and function.

DEPOSITION OF PLASMA PROTEINS IN TISSUES LEADS TO AMYLOIDOSIS

Amyloidosis refers to an impairment of tissue function that results from the accumulation of insoluble aggregates of proteins in the interstitial spaces between cells. The term is a misnomer, as it was originally thought that the fibrils were starch-like in nature. The fibrils generally are made up of proteolytic fragments of plasma proteins whose conformation is rich in **β-pleated sheet**. They generally also contain a **P component** derived from a plasma protein closely related to C-reactive protein called **serum amyloid P component**.

Structural abnormalities or overproduction of more than 20 different proteins have been implicated in various types of amyloidosis. **Primary** amyloidosis (**Table 52–7**) typically is caused by a monoclonal plasma cell disorder that leads to the accumulation of protein fragments derived from immunoglobulin **light chains** (see below). **Secondary** amyloidosis results from an accumulation of fragments of **serum amyloid A (SAA)** consequent to chronic infections or cancer. In these instances, elevated levels of inflammatory cytokines stimulate the liver to synthesize SAA, which leads to a concomitant rise in its proteolytic degradation products. **Familial amyloidosis** results from accumulation of mutated forms of certain plasma proteins such as **transthyretin** (Table 52–3). Over 80 mutationally altered forms of this protein have been identified. Patients undergoing regular, long-term dialysis are at risk from **β2-microglobulin**, a plasma protein that is retained by dialysis membranes.

TABLE 52–7 A Classification of Amyloidosis

Type	Protein Implicated
Primary	Principally light chains of immunoglobulins
Secondary	Serum amyloid A (SAA)
Familial	Transthyretin; also rarely apolipoprotein A-1, cystain C, fibrinogen, gelsolin, lysozyme
Alzheimer's disease	Amyloid β peptide (see Chapter 57, case no. 2)
Dialysis-related	β_2-microglobulin

PLASMA IMMUNOGLOBULINS DEFEND AGAINST INVADERS

The three major components of the body's immune system are **B lymphocytes (B cells), T lymphocytes (T cells)**, and **the innate immune system**. B lymphocytes are mainly derived from bone marrow cells, while T lymphocytes originate from the thymus. **B cells** are responsible for the synthesis of circulating, humoral antibodies, also known as **immunoglobulins.** The **T cells** are involved in a variety of important **cell-mediated immunologic processes** such as graft rejection, hypersensitivity reactions, and defense against malignant cells and many viruses. B and T cells respond in an **adaptive** manner, developing a targeted response for each invader encountered. The **innate immune system** defends against infection in a nonspecific manner. It contains a variety of cells such as phagocytes, neutrophils, natural killer cells, and others that will be discussed in Chapter 54.