

BIOCHEMISTRY IN PERSPECTIVE

Organelles and Human Disease



What is the role of biochemistry in modern medicine? The scientific investigation of human disease is only two hundred years old. During Europe's *Age of Enlightenment* (seventeenth and eighteenth centuries), as a result of various political and social factors combined with the discoveries of Galileo, Isaac Newton, Francis Bacon, René Descartes, and other scientists, belief systems began to change. Health concepts originating with Hippocrates (fifth century BCE) and Galen (second century CE) had been unchallenged for over a thousand years. Humoral medicine, in which health was understood in terms of a balance of the "humors" of blood, phlegm, yellow bile, and black bile, was universally accepted, and later supplemented by medieval superstition (sickness caused by divine intervention). Gradually, however, the capacity of human reason to understand the human body gained acceptance. By the end of the nineteenth century, previously unimaginable progress toward disease diagnosis and treatment had been made because of discoveries in fields ranging from anatomy, cellular pathology, and bacteriology to statistics. Today, human disease is investigated at the cellular and molecular levels because of breakthrough work performed in the 1940s and 1950s. Among the most important was the discovery of DNA as the genetic material and its subsequent structure determination (p. 636). The adaptation of the electron microscope (p. 68) by Keith Porter for use with biological specimens, and the centrifugation techniques (p. 67) developed by George Palade, Albert Claude, and Christian DeDube made the identification of distinct organelles possible. More recent work utilizing DNA technology has profoundly increased our understanding of the molecular basis of disease and vastly improved diagnostic and treatment options.

Organelles can contribute to a disease state in several ways. First, the organelle itself may be dysfunctional either because it contains one or more defective biomolecules that impair function, or because it has been damaged by exposure to harmful substances such as chemicals, heavy metals, or oxygen radicals. Second, an organelle can, through its normal function, exacerbate damage occurring elsewhere in the cell. For example, as we have seen, misfolded proteins in the ER can trigger apoptosis, even in circumstances in which it is counterproductive. The subsections that follow describe diseases associated with the endomembrane system: the ER, Golgi apparatus, vesicular organelles, the nuclear envelope, and the plasma membrane.

THE ENDOPLASMIC RETICULUM. The ER plays such a central role in the synthesis of proteins and lipids that any disturbance in its function can have serious consequences. Misfolded

proteins coded for by mutated genes and ER stress cause a vast number of diseases. Cystic fibrosis (CF) is a prominent example of a disease caused by misfolded proteins. CF is an ultimately fatal inherited disorder in which the lack of a specific type of plasma membrane chloride channel, the cystic fibrosis transmembrane regulator (CFTR), causes the accumulation of a thick mucus that compromises several organs, most notably the lungs and pancreas. The misfolded CFTR protein becomes trapped within the ER and is subsequently degraded. The structural and functional properties of CFTR are described in Chapter 11.

ER stress, induced by a variety of conditions such as protein aggregation, Ca^{2+} depletion, glucose deprivation, or fatty acid overload, can result in severe cell dysfunction or death. It is an important feature of such neurodegenerative conditions as Alzheimer's, Huntington's, and Parkinson's diseases, as well as heart disease and diabetes.

GOLGI APPARATUS. The most commonly recognized Golgi-linked diseases are a group of 15 congenital disorders of glycosylation (CDG). (The term *glycosylation* is used to describe the covalent linkage of carbohydrate groups to polypeptide or lipid molecules.) Caused by mutations in genes that encode glycosylation enzymes or glycosylation-linked transport proteins, a CDG is usually lethal by the age of 2. Symptoms include mental retardation, seizures, and liver disease.

NUCLEAR ENVELOPE. Many of the diseases attributed to defects in the nuclear envelope occur in the genes that code for lamin, a cytoskeletal component of the nuclear lamina, and emerin, an inner membrane protein. Examples include a variety of diseases of skeletal and cardiac muscle, neurons, and tendons. Progeria, a fatal childhood disease characterized by premature aging of the musculoskeletal and cardiovascular systems, has been linked to a specific mutation in the lamin A gene. One form of a rare hereditary muscular disease called Emery-Dreifuss muscular dystrophy is caused by the absence or mutation of the gene that codes for emerin. The cellular consequences of nuclear envelope deficits include a fragile nuclear membrane, altered regulation of DNA replication and transcription, and low tolerance to mechanical stress.

VESICULAR ORGANELLES. Diseases associated with vesicular organelles have been linked to lysosomes and peroxisomes. The lysosomal storage diseases (LSD) are a group of



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genetic disorders caused by the absence of one or more lysosomal enzymes. The resulting accumulation of undigested molecules causes irreversible cell damage. The lipid storage diseases Tay-Sachs and Gaucher's, as well as Pompe's disease (glycogen storage disease type II), are caused by the absence of a single enzyme. Death occurs in early childhood. In I-cell disease, the import of all lysosomal enzymes into lysosomes in certain organs is defective. In affected cells, the enzymes are instead secreted into the extracellular matrix. Symptoms include mental deterioration, heart disease, and respiratory failure.

PLASMA MEMBRANE. The plasma membrane occupies a pivotal position in the endomembrane system, as it is both the end point of the secretory pathway and the beginning of the endocytic pathway. Consequently, the PM plays important roles in a wide diversity of diseases. Diseases such as CF, diabetes, and familial hypercholesterolemia (inherited high blood cho-

lesterol levels) are directly caused by defective or missing membrane proteins. In a large number of infectious diseases, microorganisms invade body cells in endocytic processes initiated by binding to certain plasma membrane receptors. Examples of such organisms include bacteria such as *Listeria monocytogenes*, *Salmonella*, and *Shigella*, and some viruses (e.g., HIV). For viruses like HIV, which are covered in an "envelope" derived from host cell membrane, entry is gained when the virus binds to one or more PM receptors. Following fusion of the host cell membrane, and the viral envelope, the viral genome enters the host cell. Other diseases are caused when certain bacteria release toxins that injure cells. Once the toxin has become bound to a specific PM receptor on a target cell, either a pore is formed through which the toxic protein is transferred or endocytosis is triggered. Examples include cholera, pertussis (whooping cough), and diphtheria toxins.



SUMMARY: Biochemical analysis of organelles has resulted in significant progress in our understanding of the causes of many human diseases.