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Integrated Pathology

整合病理学

THOMAS C. KING

北京大学医学出版社

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整合病理学

Integrated Pathology

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出版说明

知识整合是当前医学教育改革的一项重要内容。目前国内基础医学各门课程的教材基本上是以学科为单位单独编写的，缺乏学科之间知识的联系。为了推动医学教育改革，借鉴国外医学教材的编写模式，北京大学医学出版社经过充分调研，引进出版了世界著名医学出版集团Elsevier公司的“Integrated”系列教材。

在编写上，该系列书最大的特色就是在保持本学科知识体系完整的同时插入大量的“整合框”。这些“整合框”出现在需要链接到其他学科相关知识的位置，每个学科都有独特的标识。例如在《病理学》的细胞损伤一节，讲述缺氧时，会插入一个“生物化学整合框”，介绍生物化学中糖酵解的知识；在感染一节，出现NK细胞的时候，会插入一个“免疫学整合框”，介绍免疫学中NK细胞的知识；在凝血一节，则是插入一个“临床医学整合框”，介绍临床上凝血的实验室评估方面的知识……这些分布在各本书中的“整合框”，把各学科之间知识点连接起来，不但方便了读者学习，更是体现了学科整合的理念。

该系列书包括：

●整合生理学 ●整合病理学

●整合药理学 ●整合生物化学

●整合遗传学 ●整合免疫学与微生物学

该系列书可作为国内医学生整合课程教材、双语教学教材及来华留学生教材，也有利于医学教师拓展知识，方便备课；同时也是美国医师执照考试的优秀参考用书。

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This book is dedicated to the memory of my parents,
Ernest and Violet King

Series Preface

How to Use This Book

The idea for Elsevier's Integrated Series came about at a seminar on the USMLE Step 1 exam at an American Medical Student Association (AMSA) meeting. We noticed that the discussion between faculty and students focused on how the exams were becoming increasingly integrated—with case scenarios and questions often combining two or three science disciplines. The students were clearly concerned about how they could best integrate their basic science knowledge.

One faculty member gave some interesting advice: "read through your textbook in, say, biochemistry, and every time you come across a section that mentions a concept or piece of information relating to another basic science—for example, immunology—highlight that section in the book. Then go to your immunology textbook and look up this information, and make sure you have a good understanding of it. When you have, go back to your biochemistry textbook and carry on reading."

This was a great suggestion—if only students had the time, and all of the books necessary at hand, to do it! At Elsevier we thought long and hard about a way of simplifying this process, and eventually the idea for Elsevier's Integrated Series was born.

The series centers on the concept of the *integration box*. These boxes occur throughout the text whenever a link to another basic science is relevant. They're easy to spot in the text—with their color-coded headings and logos. Each box contains a title for the integration topic and then a brief summary of the topic. The information is complete in itself—you probably won't have to go to any other sources—and you have the basic knowledge to use as a foundation if you want to expand your knowledge of the topic.

You can use this book in two ways. First, as a review book . . .
When you are using the book for review, the integration boxes will jog your memory on topics you have already covered. You'll be able to reassure yourself that you can identify the link, and you can quickly compare your knowledge of the topic with the summary in the box. The integration boxes might highlight gaps in your knowledge, and then you can use them to determine what topics you need to cover in more detail.

Second, the book can be used as a short text to have at hand while you are taking your course . . .
You may come across an integration box that deals with a topic you haven't covered yet, and this will ensure that you're one step ahead in identifying the links to other subjects (especially useful if you're working on a PBL exercise). On a simpler level, the links in the boxes to other sciences and to clinical medicine will help you see clearly the relevance of the basic science topic you are studying. You may already be confident in the subject matter of many of the integration boxes, so they will serve as helpful reminders.

At the back of the book we have included case study questions relating to each chapter so that you can test yourself as you work your way through the book.

Online Version

An online version of the book is available on our Student Consult site. Use of this site is free to anyone who has bought the printed book. Please see the inside front cover for full details on the Student Consult and how to access the electronic version of this book.

In addition to containing USMLE test questions, fully searchable text, and an image bank, the Student Consult site offers additional integration links, both to the other books in Elsevier's Integrated Series and to other key Elsevier textbooks.

Books in Elsevier's Integrated Series

The nine books in the series cover all of the basic sciences. The more books you buy in the series, the more links that are made accessible across the series, both in print and online.


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Preface

Pathology involves the investigation of the pathophysiology at the cellular and molecular levels as well as the study and characterization of diseases through the morphologic and biochemical examination of organs, tissues, and body fluids. This focus juxtaposes pathology between clinical medicine and the basic sciences. Much of the detailed features of the pathology of different organ systems can be understood in the context of basic pathophysiologic principles that apply to all cell types. This text is organized first to provide a relatively detailed introduction to these basic pathophysiologic principles (Chapters 1–5), followed by a consideration of important pathologic processes in specific organ systems (Chapters 5–14). This book should provide a comprehensive overview of important pathophysiologic mechanisms as they are understood today, but the short length of this text precludes the complete description of all diseases of each organ system. Emphasis has been placed on common diseases and diseases in which the underlying pathophysiology is becoming clearly understood or which serve as useful examples of important pathophysiologic principles. This text also emphasizes the interactions between different organ systems in disease and the necessity to consider these relationships when diagnosing and treating individual patients.

Thomas C. King, MD, PhD

Contents

Cell Injury, Cellular Responses to Injury, and Cell Death

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CONTENTS

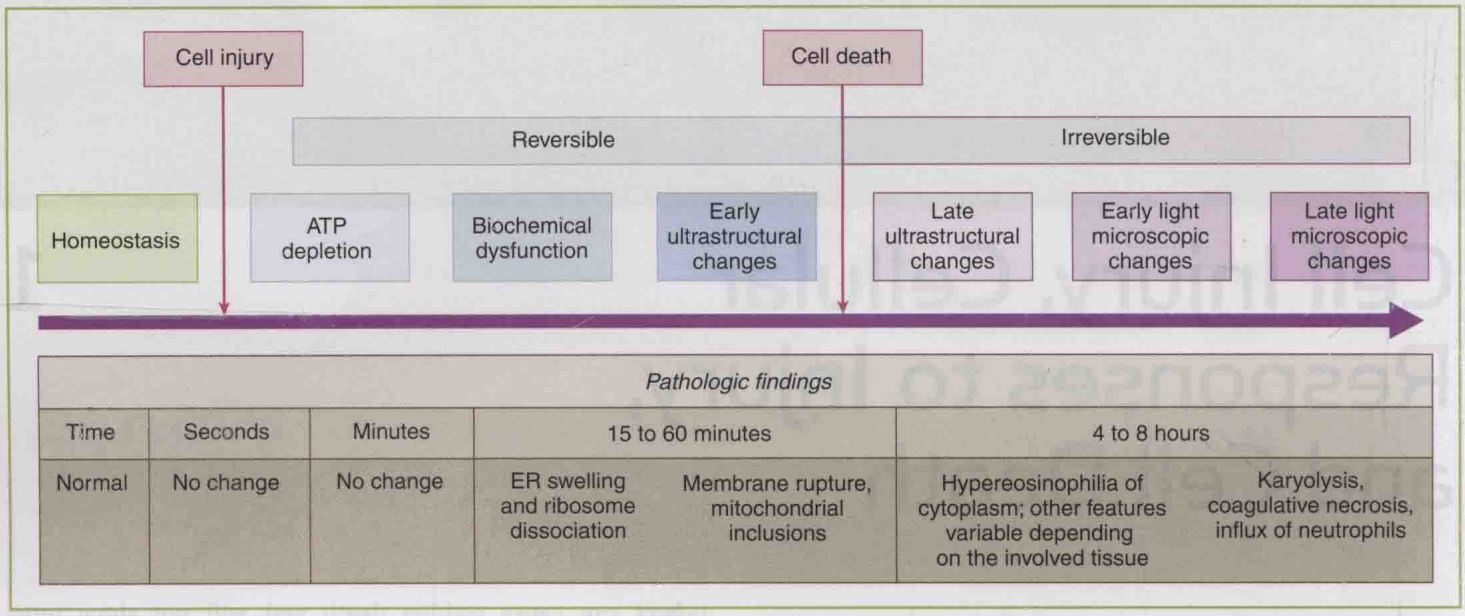
MECHANISMS OF CELL INJURY

The variety and possible mechanisms of cell injury are almost infinite, but cellular responses to various types of injury are relatively stereotyped. Indeed, many responses to injury are common to almost all types of cells, although the degree of response evoked varies considerably between different cells. Different classes of injury tend to result in relatively similar responses in a single cell type although some tissues or organs can have unique and characteristic responses to some forms of injury. Acute injuries that rapidly cause the death of an organism may not allow sufficient time for typical cellular responses to develop, so characteristic pathologic changes may be minimal or absent. For example, an acute myocardial infarct can cause sudden death and will not show morphologic features of myocyte necrosis because death occurs before the body can respond to this injury.

Cell injury that is severe enough to cause cell death tends to evolve through a series of biochemical and morphologic changes that follow a relatively consistent time scale. Ischemic injury (see Ischemia section) resulting from the occlusion of a tissue's vascular supply is a useful example to illustrate the changes that develop as cells respond to severe injury (Fig. 1-1). Biochemical changes develop within seconds to minutes after injury with marked depletion of intracellular ATP.

Morphologic changes are not apparent by electron microscopy until at least 10 minutes after injury with swelling of the endoplasmic reticulum and dissociation of ribosomes from the rough endoplasmic reticulum. These changes develop directly as a consequence of ATP depletion. Loss of ATP also results in the degradation of ionic gradients across cell membranes because ion pumps are no longer supplied with energy. These changes may be reversed if blood supply is rapidly restored to the injured cells.

Rupture and fragmentation of plasma and organelle membranes (which can be observed by electron microscopy but not by light microscopy) are a signal that irreversible injury has occurred. Approximately 15 minutes after the onset of severe ischemic injury, there is a large influx of calcium into damaged cells through membrane tears. Calcium entry activates lipases and proteases that begin to autodigest the irreversibly injured cell (Fig. 1-2). Light microscopic evidence of cell injury appears well after ultrastructural changes are well developed (usually hours after ischemic injury). These light microscopic changes correspond to the evolution of coagulative necrosis (discussed in detail below). The time scale of these events depends critically on the metabolic activity of the injured cell. Very active cells deplete ATP more quickly (e.g., proximal tubular cells in the kidney) and can undergo irreversible injury within a few minutes, whereas quiescent cells (e.g., collecting duct epithelia in the kidney) may survive more prolonged episodes of ischemia.



Pathologic findings						
Time	Seconds	Minutes	15 to 60 minutes		4 to 8 hours	
Normal	No change	No change	ER swelling and ribosome dissociation	Membrane rupture, mitochondrial inclusions	Hypereosinophilia of cytoplasm; other features variable depending on the involved tissue	Karyolysis, coagulative necrosis, influx of neutrophils

Figure 1-1. Time scale of reversible and irreversible cell injury.

BIOCHEMISTRY

Oxidative Phosphorylation

Oxidative phosphorylation occurs in mitochondria and involves five protein complexes as well as electron carriers coenzyme Q and cytochrome c, all of which are embedded in the inner mitochondrial membrane.

These complexes catalyze reactions that sequentially liberate energy and result in the translocation of protons through the inner membrane to create a pH gradient.

This pH gradient is then used to synthesize ATP from ADP by the passage of H^+ protons out of the inner membrane.

- Complex I converts NADH to NAD^+ with the translocation of 2 H^+ protons.
- Complex II and III convert succinate to fumarate and translocate 4 H^+ protons.
- Complex IV converts ½ oxygen molecule to water and translocates 2 H^+ protons.
- Complex V allows reverse passage of 3 H^+ protons down the concentration gradient with the synthesis of one ATP molecule in the mitochondrial matrix.

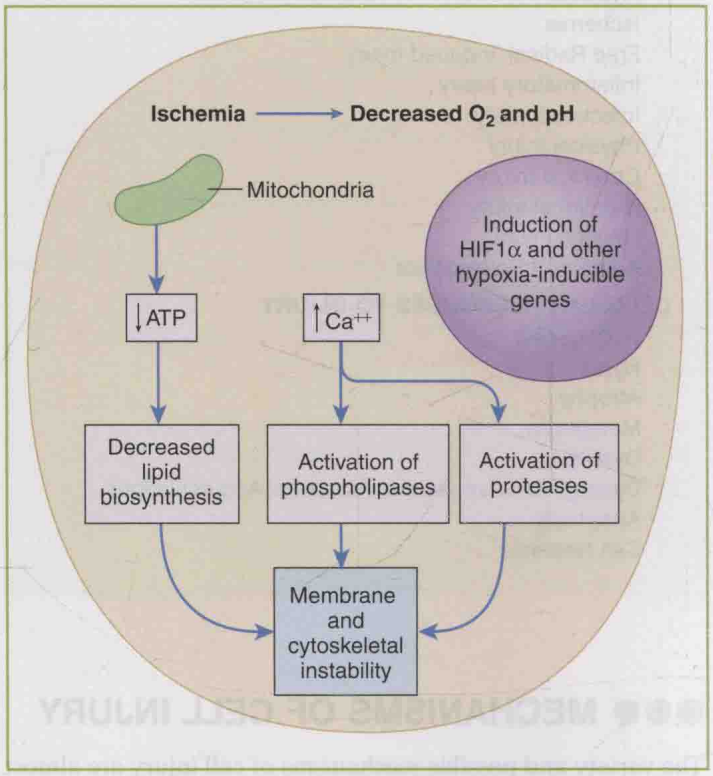


Figure 1-2. Biochemical alterations in ischemic injury.

Hypoxia

Hypoxic injury implies damage to cells resulting only from decreased oxygen tension. This is a relatively unusual pattern of injury in its pure form. Hypoxia can result from decreased atmospheric oxygen concentration, abnormal lung function, and decreased oxygen-carrying capacity in the blood (e.g., severe anemia). Acute hypoxia results in depletion of ATP in cells that triggers a switch to anaerobic glycolysis.

Since the energy yield from glycolysis is much less than from oxidative phosphorylation, energy demands are not met and the continuing decrease in ATP levels results in additional cellular dysfunction. Increased lactic acid produced by glycolysis also decreases intracellular pH, resulting in additional dysfunction.

As discussed above, different types of cells have markedly different metabolic rates and cells with high metabolic rates tend to be injured or killed very rapidly by hypoxia. For example, proximal tubular cells in the kidney may undergo necrosis (acute tubular necrosis, ATN) as a result of even transient hypoxia (Fig. 1-3). The light microscopic changes

associated with necrosis include condensation and shrinking (pyknosis) or disappearance (karyolysis) of cell nuclei, which is evident in the necrotic renal tubular cells in Figure 1-3. These cells also show increased eosin staining (hypereosinophilia) of their cytoplasm as a result of the degradation of cellular proteins and loss of cytoplasmic RNA. Other cell types (e.g., neurons) may initiate apoptosis in response to hypoxic injury (see Apoptosis section). Chronic, sublethal hypoxia can activate transcription of genes that can initiate angiogenesis (new blood vessel formation), resulting in neovascularization of the affected tissue.

BIOCHEMISTRY

Glycolysis

Glycolysis metabolizes glucose and rapidly produces a small amount of ATP as well as acid, pyruvate, and NADH that can feed into the Krebs cycle. The overall reaction is

$$\text{Glucose} + 2\ \text{ADP} + 2\ P_i + 2\ NAD^+ \rightarrow$$
$$2\ \text{pyruvate} + 2\ \text{ATP} + 2\ \text{NADH} + 2\ H^+ + 2\ H_2O$$

Metabolism of glycolysis end products in the Krebs cycle produces much larger amounts of ATP than glycolysis does. In the absence of oxygen, the Krebs cycle is not active and acid and pyruvate can quickly accumulate. Since the amount of ATP produced from glucose by glycolysis is quite small relative to oxidative phosphorylation, energy charge declines rapidly in most hypoxic cells even if large glucose stores are available.

Ischemia

Ischemic injury is caused by diminished or absent blood flow. The main mechanism of injury in ischemia is hypoxia (as described above). Ischemic injury also results in more rapid and severe cellular acidosis than pure hypoxic injury because the absence of blood flow causes the localized accumulation of cellular metabolic by-products (e.g., lactic acid from anaerobic glycolysis). Ischemia may be relative or complete, in which case it usually results in coagulative necrosis. Relative ischemia can occur as a result of low blood pressure (hypotension), marked increases in cellular metabolism, and vascular stenosis. Relative ischemia typically results in cellular dysfunction but does not cause death in most cell types. Some cell types that are more sensitive to ischemic damage (e.g., neurons) may undergo apoptosis or necrosis while other cell types remain viable. Complete ischemia most often results from blockage of an arterial branch that causes infarction of the tissue supplied by that blood vessel. If an occluded blood vessel is reopened soon after ischemic injury, reversibly injured cells may recover. This situation is referred to as reperfusion and has become more common in the setting of myocardial infarction treated emergently by angioplasty and thrombolysis. Reperfusion may be too late to permit recovery of irreversibly injured cells and is often associated with hemorrhage owing to ischemic damage to endothelial cells in blood vessels that occurs prior to restoration of blood flow.

Free Radical–Induced Injury

Free radicals are active chemical compounds that can react directly with proteins, lipids, and DNA. Biologic free radicals

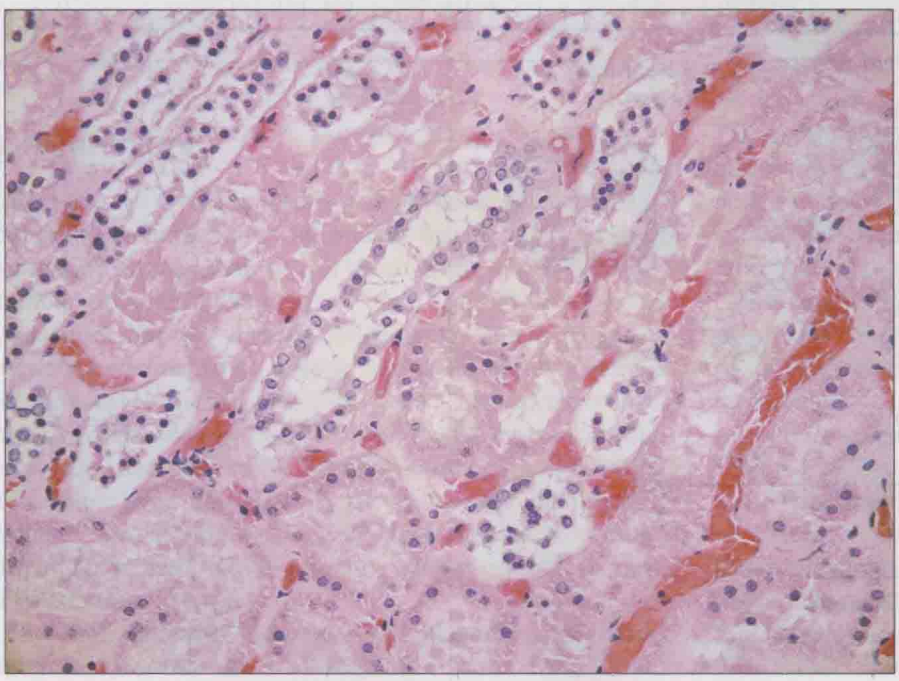


Figure 1-3. Acute tubular necrosis in the kidney. Note the eosinophilic staining of proximal tubular cells with loss of nuclear staining. The high metabolic rate of proximal tubular cells results in their rapid necrosis under ischemic or hypoxic conditions. Less active distal tubule and collecting duct epithelial cells appear morphologically normal in this photomicrograph.

are generated predominantly from oxygen metabolism. High oxygen tension and increased oxidative phosphorylation favor the formation of free radicals and can lead to severe cellular injury if protective mechanisms are not effective. Cellular macromolecules that react chemically with free radicals (phospholipids and proteins) often lose their normal function and cannot be repaired. These oxidized macromolecules are not effectively degraded by lysosomal enzymes, and oxidized protein and lipid fragments tend to accumulate in cells with free radical damage. These oxidized macromolecules tend to aggregate to form lipofuscin pigment that is retained in the damaged cell and provides an indication of the degree of oxidative stress a cell has experienced. Oxidative phosphorylation and β–fatty acid oxidation in mitochondria produce significant oxidative stress that may result in mitochondrial damage and trigger apoptosis by releasing mitochondrial proteins (e.g., cytochrome c) into the cytoplasm.

Specific enzyme systems are present in all cells to react with and detoxify free radicals. Superoxide dismutase (SOD) and catalase are important components of this system (Fig. 1-4). Cells that are frequently exposed to oxidative stress (high oxygen tension, very active oxidative phosphorylation, or β-oxidation of fatty acids) tend to express these enzyme systems at higher levels. Glutathione is another important protectant from free radical damage. Sulfhydryl groups on glutathione act as free radicals scavengers, and oxidation of glutathione can prevent damage to key cellular components. Hepatocytes contain relatively large amounts of glutathione to manage oxidative stress from the metabolism of various compounds and drugs by their cytochrome P-450 enzymes. Depletion of glutathione renders hepatocytes sensitive to free radical damage that can result in massive hepatic necrosis (e.g., acetaminophen poisoning). β-Carotene and other vitamins can act as free radical scavengers and may assist in detoxifying free radicals.

Inflammatory Injury

Inflammatory cells are very important in the response to injury in all tissues. Inflammation is the primary host response to infection, but it is also an essential component of the response to most other forms of injury. One consequence of the recruitment of inflammatory cells is the generation of large amounts of oxygen-derived free radicals by these cells. Cytokines, growth factors, and degradative enzymes also are produced and released into the extracellular environment by inflammatory cells. These molecules and proteins can damage parenchymal cells in inflamed tissues and may lead to cell death. Other forms of immune-mediated injury caused by antibodies and activated T cells may directly damage or kill parenchymal cells (e.g., viral infection and autoimmune disease; Fig. 1-5).

Infectious Injury

Infectious agents can damage cells and tissues directly by the production of toxins and/or degradative enzymes. Viruses directly infect host cells and may produce cell dysfunction or death. In addition to their direct effects, almost all infectious agents stimulate an immune and/or inflammatory response that can cause severe cellular damage.

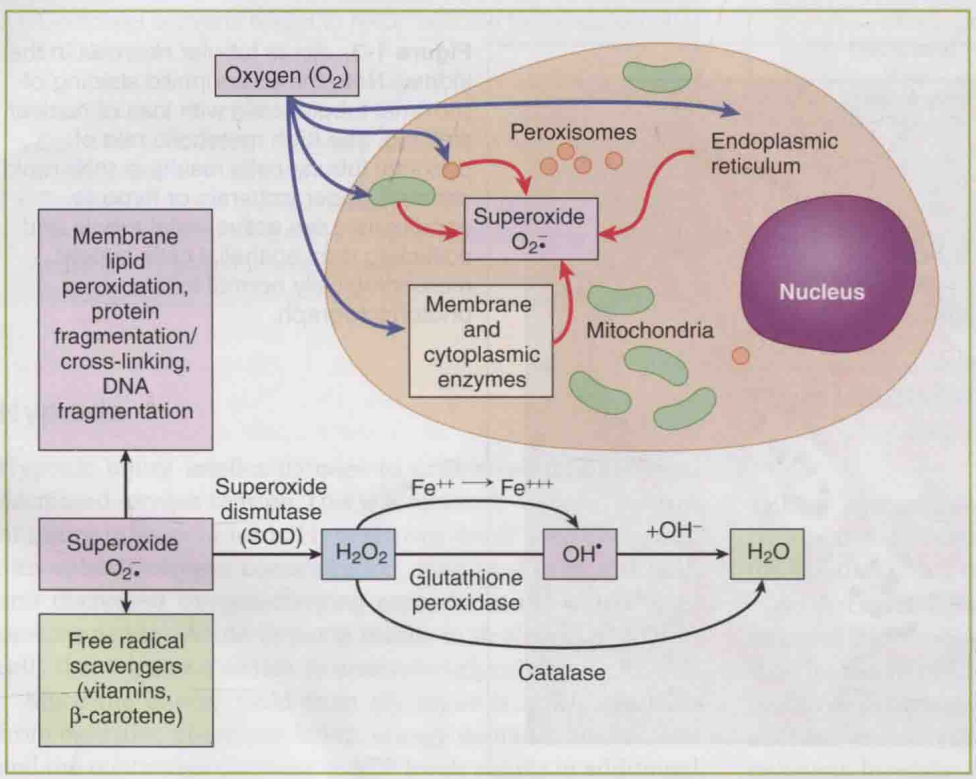


Figure 1-4. Generation, production, and detoxification of oxygen free radicals.

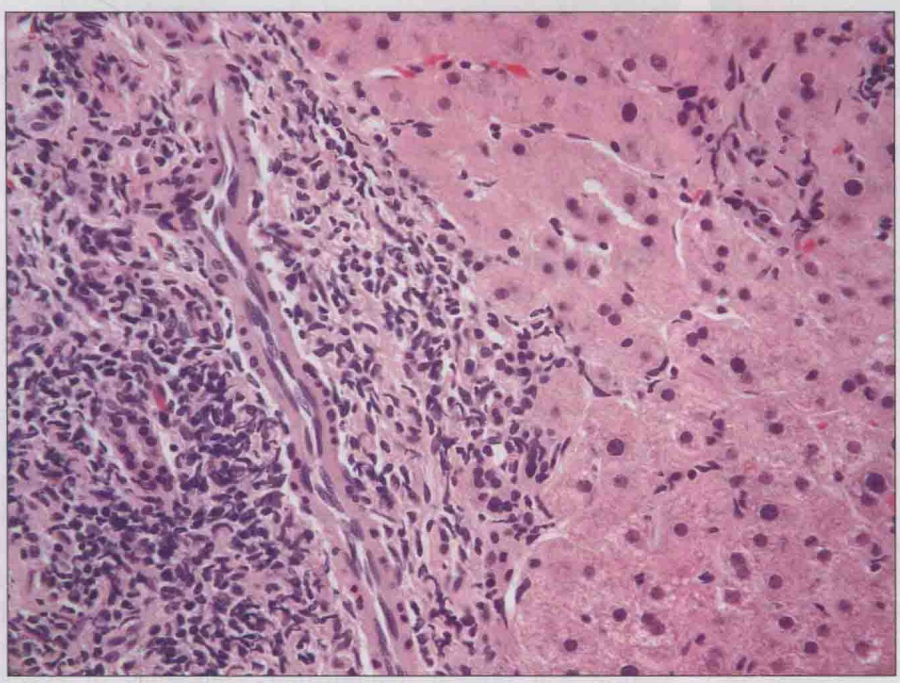


Figure 1-5. Immune-mediated injury in the liver. Microscopic section from a case of chronic hepatitis C virus infection showing piecemeal necrosis at the periphery of a portal tract. Individual hepatocytes are surrounded by T cells that trigger them to undergo apoptosis.

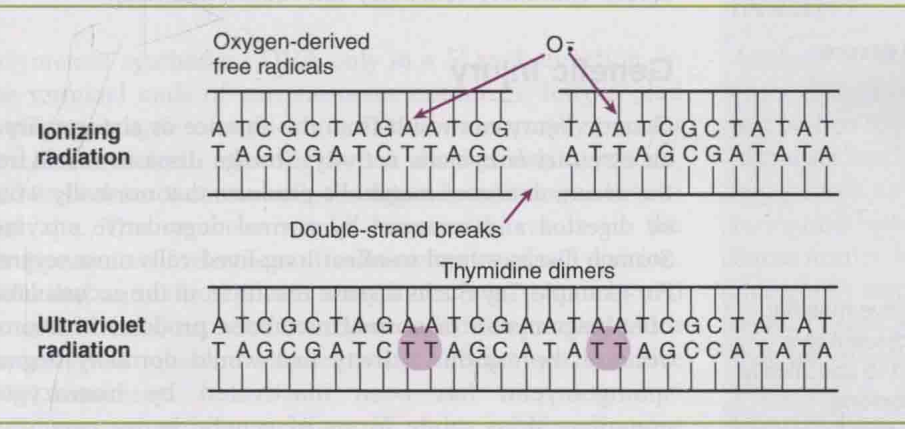


Figure 1-6. Radiation-induced injury.

Physical Injury

Physical injury typically refers to mechanical trauma but additionally includes injury secondary to solar and ionizing radiation. Mechanical injury can result from projectiles such as bullets, penetrating trauma, or blunt trauma. Trauma can initiate infection by directly introducing microorganisms (penetrating trauma) or by causing the breaks in host defenses (skin, mucosal surfaces, or intestinal tract perforation). Trauma can also damage tissues and organs by transmitting energy (e.g., deceleration of a bullet passing through tissue can transfer large amounts of kinetic energy resulting in damage to or destruction of a large tissue volume around the bullet track). In addition, trauma can result in vascular damage that causes hemorrhage.

Ultraviolet radiation can damage collagen to the extracellular matrix, but its main toxicity results from direct interaction with DNA to form thymidine dimers (Fig. 1-6). Thymidine dimers may trigger apoptosis if they are not effectively repaired, or cell division may result in mutations in daughter cells. Damage from ultraviolet radiation is limited to exposed skin and mucous membranes, whereas ionizing radiation can penetrate deep within the body.

Ionizing radiation can produce free radicals by interaction with water molecules, or it may directly interact with DNA, resulting in single- and double-strand breaks that may not be repairable.

High levels of ionizing radiation can be acutely fatal because of severe free radical damage to neurons while somewhat lower doses can result in death subacutely because of extensive damage to replicating progenitor cells (e.g., gastrointestinal tract and bone marrow). The rapid cycling of progenitor cells means that a high percentage are undergoing replication at all times. After radiation injury, there is insufficient time for most progenitor cells to repair DNA damage before they enter the cell cycle. These cells then

PHYSIOLOGY

Radiation Therapy

Ionizing radiation can be delivered as electromagnetic energy (waves) or as particles (usually electrons) with external beam therapy. External beam is the most commonly employed form of radiation therapy, in which a collimated beam of irradiation or particles is produced from a radiation source (isotope, accelerator, etc.) and directed at a tumor.

Charged particles can directly interact with and alter or destroy the molecular structure of cellular macromolecules to provide an antitumor effect. Electromagnetic radiation and neutrons are indirectly ionizing and must interact with water molecules in tissue to generate high-energy charged particles that ultimately cause cellular damage.

Conformal mapping is a sophisticated form of treatment planning that directs irradiation at a tumor from many different directions to maximize tumor dose while minimizing the dose to sensitive tissues (e.g., the radiation beam to treat a central tumor in the abdomen is radially targeted from the front, back, and sides of the patient to limit skin, intestinal, and spinal cord toxicity).

Fractionation of irradiation means dividing radiation doses into a series of smaller additive doses that are administered over a time interval to decrease toxicity to normal tissues. Normal tissues vary greatly in sensitivity to ionizing radiation (which is measured in centigrays, cGy).

Radiation dose resulting in 50% incidence of severe toxicity/loss of function

Testis	200 cGy
Eye	1200 cGy
Lung	3000 cGy
Bone marrow	5000 cGy
Spinal cord	6000 cGy
GI tract	6000 cGy

Brachytherapy is performed by inserting radioactive material (radioactive seeds or needles) directly into or adjacent to a tumor. Injected radioactive isotopes can be used to specifically target tumor cells if they are conjugated to monoclonal antibodies or are specifically taken up by tumor cells (e.g., radioactive iodine is used in thyroid cancer).

either trigger apoptosis or propagate mutations in their daughter cells. Loss of progenitor cells causes the breakdown of the mucosal layer after hours to days as well as marked myelosuppression with bone marrow failure over the course of days.

Chemical Injury

Chemical injury ranges from direct damage to cells and tissues by caustic agents (e.g., strong acid or bases) to damage due to toxins that may have very specific targets in a limited number of cell types (e.g., organophosphate compounds that simulate neurotransmitters in neurons, causing uncontrolled depolarization that can lead to cell death). Some chemicals result in the production of toxic substances (e.g., free radical production in hepatocytes) that are the ultimate mediators of injury. Many chemicals and drugs must be metabolized (usually by the liver's cytochrome P-450 system) before they are toxic to cells. Genetic polymorphisms in these drug-metabolizing enzymes in each individual can result in great differences in the effective doses of drugs and in the potential to generate toxic metabolites from various compounds.

Nutritional Injury

Nutritional injury corresponds to a lack of adequate intake of calories or protein that results in cellular or tissue dysfunction. Caloric malnutrition impairs a cell's ability to generate ATP and to maintain normal cellular functions. Protein malnutrition with adequate caloric intake can result in the inability to synthesize normal cellular proteins because of an inadequate amount of essential amino acids (i.e., amino acids that cannot be synthesized de novo). The consequences of nutritional injury differ greatly in children and adults. Growth retardation in children may be irreversible. The developing nervous system is particularly sensitive to both calorie and protein malnutrition. Deficiency of essential vitamins can lead to marked cellular dysfunction, which may cause irreversible damage to some specialized cells (e.g., severe vitamin A deficiency can cause blindness).

Genetic Injury

Genetic injury can result from the absence or abnormality of an essential enzymatic activity. Storage diseases result from the accumulation of metabolic products that normally would be digested and removed by normal degradative enzymes. Storage diseases tend to affect long-lived cells most severely. For example, Tay-Sachs disease results from the accumulation of sphingomyelin (a normal metabolic product) in neurons because the enzyme activity that would normally degrade sphingomyelin has been inactivated by homozygous mutation. More subtle forms of genetic injury may result from changes in cellular metabolism that predispose to, or accelerate, different types of disease (e.g., deficiency of the low-density lipoprotein receptor results in markedly increased cholesterol levels in blood that greatly accelerate atherosclerosis). Genetic polymorphisms can cause more subtle disease predispositions (see Chapter 4).

Aging and Senescence

Normal aging is not usually considered a pathologic condition although dysfunctional changes associated with cellular aging are not always distinct from disease processes. Aging almost always results in a decreased capacity of cells to proliferate and to respond to injury. Cells from older individuals have decreased replicative capacity because of age-dependent shortening of the length of telomeres at the ends of their chromosomes. Telomeres consist of numerous repeats of the sequence $TTAGGG_n$ and are on the order of 5 to 15 kilobases in length in normal cells in young individuals. DNA

BIOCHEMISTRY

Telomerase Enzymatic Structure

Chromosomal telomeres range from 5 to 15 kilobases in length in normal cells in younger individuals. As a consequence of the 3′ → 5′ directionality of DNA polymerase, approximately 50 to 200 nucleotides of telomere sequence are lost from the lagging DNA strand during cell division. If these lost sequences are not replaced, cells become unable to initiate S phase after approximately 60 to 70 doublings (the so-called Hayflick limit). Telomerase can replace these sequences and restore telomeres to full length to prevent cellular senescence.

Telomerase is a ribonucleoprotein complex that consists of the TERT (telomerase reverse transcriptase) protein (130 kD) and the TERC (telomerase RNA component) in combination with several smaller accessory proteins including GAR1 and dyskerin that are all required for normal telomerase function. The TERC has a stem loop structure that provides the template sequence (CCCTAA) that codes for synthesis of telomere repeats.

Mutations or deletions in any of these proteins or in the TERC can cause loss of telomerase function and result in cellular senescence.

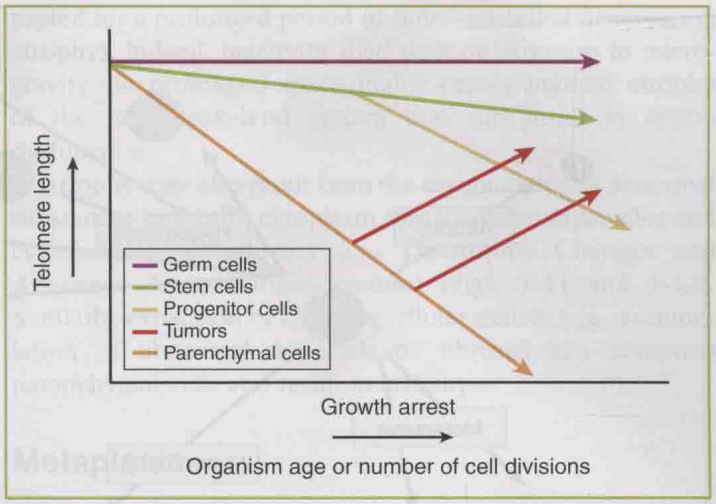


Figure 1-7. Maintenance of telomere length in different cell types.

polymerase synthesizes DNA only in a 5′ to 3′ direction, so the terminal ends of chromosomes cannot be fully copied during each cycle of replication. Telomeres normally prevent chromosomes from adhering to one another during mitosis, and their absence causes cells to trigger apoptosis (see below) and die. This process would eventually result in the disappearance of telomeres after many cycles of cell division. Cells that normally replicate many times (e.g., stem cells and progenitor cells) express an enzyme called telomerase, which replaces lost telomere sequences by adding new repetitive DNA sequences.

Telomerase activity declines in most cells with aging (Fig. 1-7), resulting in age-dependent telomere shortening that ultimately results in growth arrest (senescence). Normal stem cells continue to express telomerase and maintain telomere length. Genetic abnormalities in telomerase can cause stem cell failure resulting in some cases of aplastic anemia (see Chapter 11). Telomerase expression is frequently reactivated in malignant tumors, allowing them to escape from growth control by senescence.

Accumulated free radical stress in mitochondria can lead to dysfunction that may result in decreased energy production or trigger apoptosis. Apoptosis of permanent cells results in permanent loss of function, and this mechanism may also be important in aging. Higher caloric intake in lower animals is known to result in a shorter life span, and mitochondrial stress may explain these results.

Some of the changes observed in normal aging are accelerated in specific pathologic conditions (e.g., Alzheimer's disease), and this acceleration usually is considered pathologic (e.g., familial Alzheimer's disease). A few rare genetic syndromes (e.g., progeria) result in the rapid senescence of many tissues that resembles normal aging but results in death in childhood.

CELLULAR RESPONSES TO INJURY

Analysis of cellular and tissue responses to injury is the core of the discipline of pathology. Because cells and organ systems respond to insults in a relatively stereotyped manner, these responses can be used to infer the cause or nature of injury in many cases. Cellular responses include dysfunctional changes in injured cells as well as inflammation in response to different insults. Many cells undergo (compensatory or adaptive) changes in response to injury or alterations in their environment. Tissues and organs can also undergo adaptive changes that are coordinated to manage internal or environmental stresses (e.g., alterations in heart rate and blood pressure). Coordination of these changes can occur at many levels including cell-cell interactions, localized signaling (paracrine signaling), and hormonal and neural signaling. The detailed repertoire of responses of different cells and tissues to different forms of injury occupies the bulk of later chapters in this text. Some basic mechanisms of response to injury are shared by most cell types and serve as a basis for understanding the more complicated responses of tissues and organs. These basic mechanisms include hyperplasia, hypertrophy, metaplasia, and atrophy (Fig. 1-8).

Hyperplasia

Hyperplasia is an increase in cell number (due to cell replication) in response to various stimuli. For some cell types (so-called "labile tissues"), replication is constantly required to replace lost cells (e.g., replication of basal cells in the skin provides a constant supply of new cells to replace those desquamated from the surface and is essential to maintain a steady state). Hyperplasia in a labile tissue can be accom-

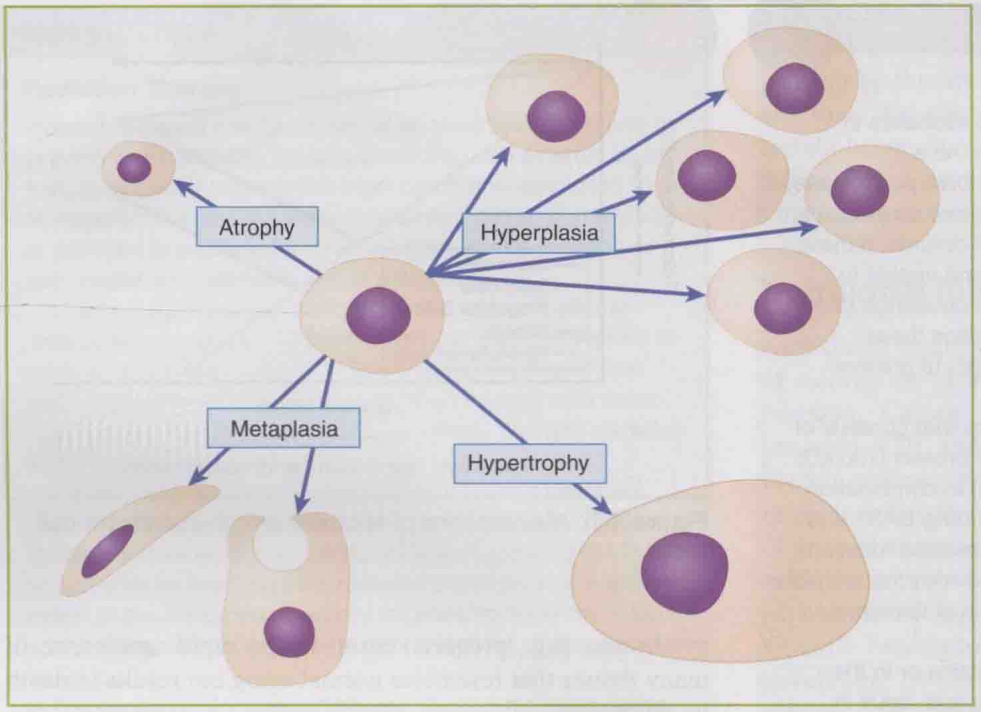


Figure 1-8. Mechanisms of cellular adaptation.

Labile	Stable	Permanent
(constant active self-renewal)	(low level of renewal with capacity to replace cells)	(no capacity to replace cells)
Gastrointestinal mucosa	Liver	Adult neurons
Skin	Renal tubular cells	Renal glomeruli
Hematopoietic cells	Glial cells in the CNS	Retinal epithelial cells

Figure 1-9. Properties of labile, stable, and permanent tissues.

plished by increasing the replicative rate of precursor cells or by recruiting additional cells into the replicating pool. Increased proliferation may maintain steady state in the face of increased cell loss or may lead to a net increase in the number of mature cells present. "Stable tissues" have a much lower rate of cell turnover in steady state and so require a much lower rate of cell division to maintain homeostasis under normal conditions. Many stable tissues such as the liver retain a robust capacity for hyperplasia in response to injury or destruction of parenchymal cells (Fig. 1-9). These stable tissues have the capacity to greatly increase the number of replicating progenitor cells to replace cells destroyed by various forms of injury. When the injury has been repaired, the replicative rate usually diminishes to maintain a steady-state number of parenchymal cells. A third type of tissue often is called "permanent tissue" because its parenchymal cells have no capacity for hyperplasia or self-renewal in response to injury. The parenchymal cells in permanent tissues (e.g., neurons in the adult central nervous system and cardiac myocytes) are long-lived cells that can survive throughout a person's lifetime under normal conditions. If these cells are destroyed, however, there is no normal, effective way to replace them (although there may be the potential to artificially manipulate stem cells to replace some types of "permanent" cell).

Sustained hyperplasia in response to chronic injury can strain the replicative capacity of a tissue. The progenitor pool may become inadequate to manage demand for new cells, or nutritional demands to support cell replication (vitamins, amino acids, calories) may not be met. Marked and prolonged hyperplasia may also predispose to the development of genetic abnormalities in cells that may eventually lead to unregulated cell growth (i.e., dysplasia and neoplasia; see below). Hyperplasia by itself may produce significant dysfunction (e.g., nodular hyperplasia of the prostate gland tends to block urine flow, leading to urinary retention and bladder infection, and metabolic syndromes can result from hyperplasia of endocrine organs).

Hypertrophy

Hypertrophy is an increase in the size of cells (or tissues) in response to various stimuli. A typical example is muscular hypertrophy in response to exercise. Exercise stimulates