KEY CONCEPTS

Abnormal Intracellular Depositions and Calcifications

Abnormal deposits of materials in cells and tissues are the result of excessive intake or defective transport or catabolism.

- **Deposition of lipids**
  - Fatty change: Accumulation of free triglycerides in cells, resulting from excessive intake or defective transport (often because of defects in synthesis of transport proteins); manifestation of reversible cell injury
  - Cholesterol deposition: Result of defective catabolism and excessive intake; in macrophages and smooth muscle cells of vessel walls in atherosclerosis
- **Deposition of proteins:** Reabsorbed proteins in kidney tubules; immunoglobulins in plasma cells
- **Deposition of glycogen:** In macrophages of patients with defects in lysosomal enzymes that break down glycogen (glycogen storage diseases)
- **Deposition of pigments:** Typically indigestible pigments, such as carbon, lipofuscin (breakdown product of lipid peroxidation), or iron (usually due to overload, as in hemosiderosis)
- **Pathologic calcifications**
  - Dystrophic calcification: Deposition of calcium at sites of cell injury and necrosis
  - Metastatic calcification: Deposition of calcium in normal tissues, caused by hypercalcemia (usually a consequence of parathyroid hormone excess)

Cellular Aging

Mankind has pursued immortality from time immemorial. Toth and Hermes, two Egyptian and Greek deities, are said to have discovered the elixir of youth and become immortal. Sadly, despite intense search, that elixir is nowhere to be found. Shakespeare probably characterized aging best in his elegant description of the seven ages of man. It begins at the moment of conception, involves the differentiation and maturation of the organism and its cells, at some variable point in time leads to the progressive loss of functional capacity characteristic of senescence, and ends in death.

Individuals age because their cells age. Although public attention on the aging process has traditionally focused on its cosmetic manifestations, aging has important health consequences, because age is one of the strongest independent risk factors for many chronic diseases, such as cancer, Alzheimer disease, and ischemic heart disease. Perhaps one of the most striking discoveries about cellular aging is that it is not simply a consequence of cells "running out of steam," but in fact is regulated by genes that are evolutionarily conserved from yeast to worms to mammals.

Cellular aging is the result of a progressive decline in cellular function and viability caused by genetic abnormalities and the accumulation of cellular and molecular damage due to the effects of exposure to exogenous influences (Fig. 2-35). Studies in model systems have clearly established that aging is influenced by a limited number of genes, and genetic anomalies underlie syndromes resembling premature aging in humans as well. Such findings suggest that aging is associated with definable mechanistic alterations. Several mechanisms, some cell intrinsic and others environmentally induced, are believed to play a role in aging.

DNA Damage. A variety of exogenous (physical, chemical, and biologic) agents and endogenous factors such as ROS threaten the integrity of nuclear and mitochondrial DNA. Although most DNA damage is repaired by DNA repair enzymes, some persists and accumulates as cells age. Several lines of evidence point to the importance of DNA repair in the aging process. Next generation DNA sequencing studies have shown that the average hematopoieitic stem cell suffers 14 new mutations per year, and it is likely that this accumulating damage explains why, like most cancers, the most common hematologic malignancies are diseases of the aged. Patients with *Werner syndrome* show premature aging, and the defective gene product is a DNA helicase, a protein involved in DNA replication and repair and other functions requiring DNA unwinding. A defect in this enzyme causes rapid accumulation of chromosomal damage that may mimic the injury that normally accumulates during cellular aging. Genetic instability in somatic

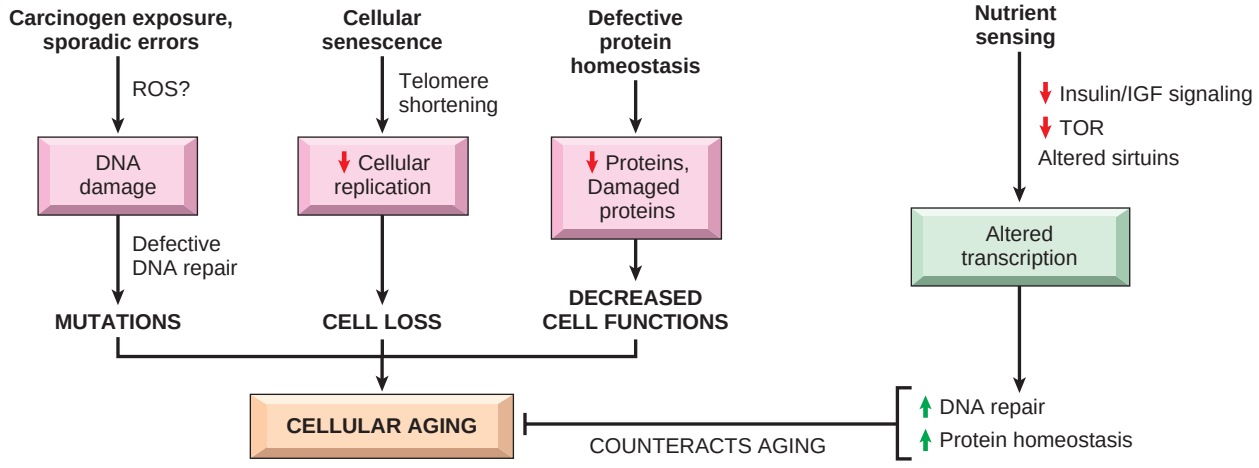

Figure 2-35 Mechanisms that cause and counteract cellular aging. DNA damage, replicative senescence, and decreased and misfolded proteins are among the best described mechanisms of cellular aging. Nutrient sensing exemplified by calorie restriction, counteracts aging by activating various signaling pathways and transcription factors. IG, Insulin-like growth factor; TOR, target of rapamycin.