Lec 3

General Pathology

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PhD. Oral Pathology

Intracellular Accumulations

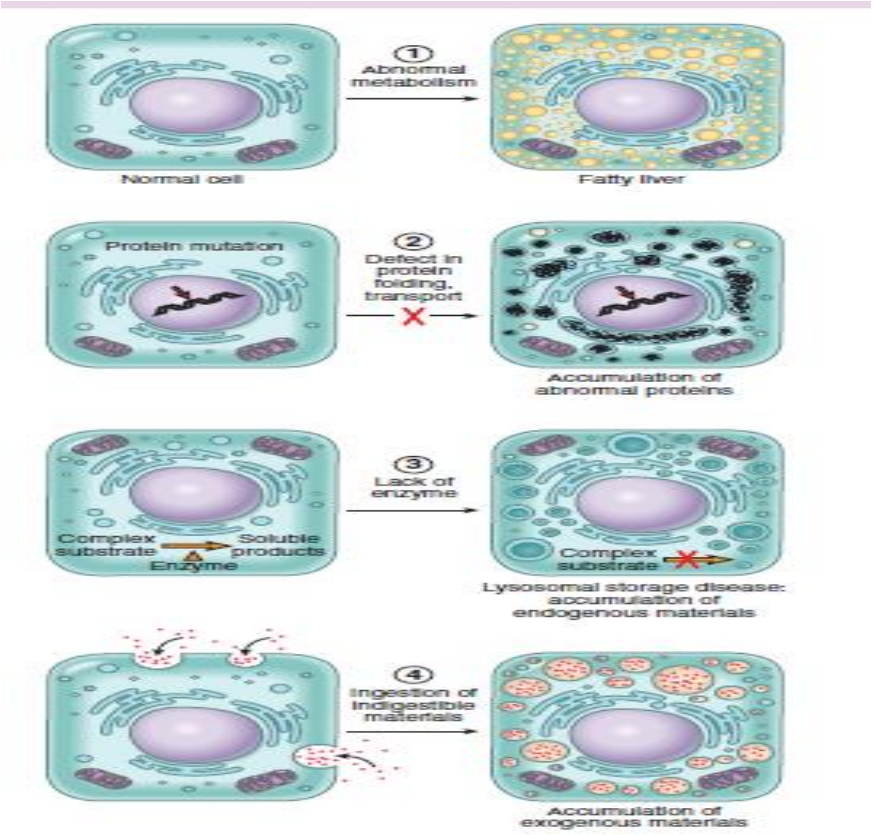
One of the manifestations of metabolic derangements in cells is the *intracellular accumulation* of substances that may be harmless or cause further injury.

These accumulations may be located in the cytoplasm, within organelles (typically lysosomes), or in the nucleus, and they may be composed of substances that are synthesized by the affected cells or are produced elsewhere.

Mechanism of Intracellular Accumulations:

There are four main mechanisms leading to abnormal intracellular accumulations:

- ***Inadequate removal* of a normal substance secondary to defects in packaging and transport, as in fatty change (steatosis) in the liver.**
- **Accumulation of an endogenous substance as a result of genetic or acquired defects in its folding, packaging, transport, or secretion, as with certain mutated forms of α1-antitrypsin.**
- **Failure to degrade a metabolite due to inherited enzyme deficiencies, typically lysosomal enzymes. The resulting disorders are called lysosomal storage diseases.**
- **Deposition and accumulation of an abnormal exogenous substance when the cell has neither the enzymatic machinery to degrade the substance nor the ability to transport it to other sites. Accumulation of carbon or silica particles is an example of this type of alteration.**



ABNORMAL INTRACELLULAR DEPOSITIONS AND CALCIFICATIONS:

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

1. **Deposition of lipids**
   a. **Fatty change: Accumulation of free triglycerides in cells, resulting from excessive intake or defective transport (often because of defects in the synthesis of transport proteins); manifestation of reversible cell injury.**
   b. **Cholesterol deposition: Result of defective catabolism and excessive intake; in macrophages and smooth muscle cells of vessel walls in atherosclerosis.**
2. **Deposition of proteins: Reabsorbed proteins in kidney tubules; immunoglobulins in plasma cells.**
3. **Deposition of glycogen: In macrophages of patients with defects in lysosomal enzymes that break down glycogen (glycogen storage diseases) and in certain disorders of glycogen metabolism.**
4. **Deposition of pigments: Typically, indigestible pigments, such as carbon (exogenous), and endogenous deposits like lipofuscin (a breakdown product of lipid peroxidation), melanin (brown-black, pigment deposited in the skin, connective tissue, and cartilage), or iron (usually due to overload, as in hemosiderosis).**
5. **Pathologic calcifications**
   a. **Dystrophic calcification: Deposition of calcium at sites of cell injury and necrosis,**

b. Metastatic calcification: Deposition of calcium in normal tissues, caused by hypercalcemia (usually a consequence of parathyroid hormone excess.

CELLULAR AGING:

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.

Mechanism of Cellular Aging:

1. **Accumulation of DNA damage: Defective DNA repair mechanisms; conversely, caloric restriction may activate DNA repair and slow aging in model organisms.**
2. **Replicative senescence: Reduced capacity of cells to divide secondary to progressive shortening of chromosomal ends (telomeres).**
3. **Defective protein homeostasis**
4. **Nutrient sensing system: Caloric restriction increases longevity.**

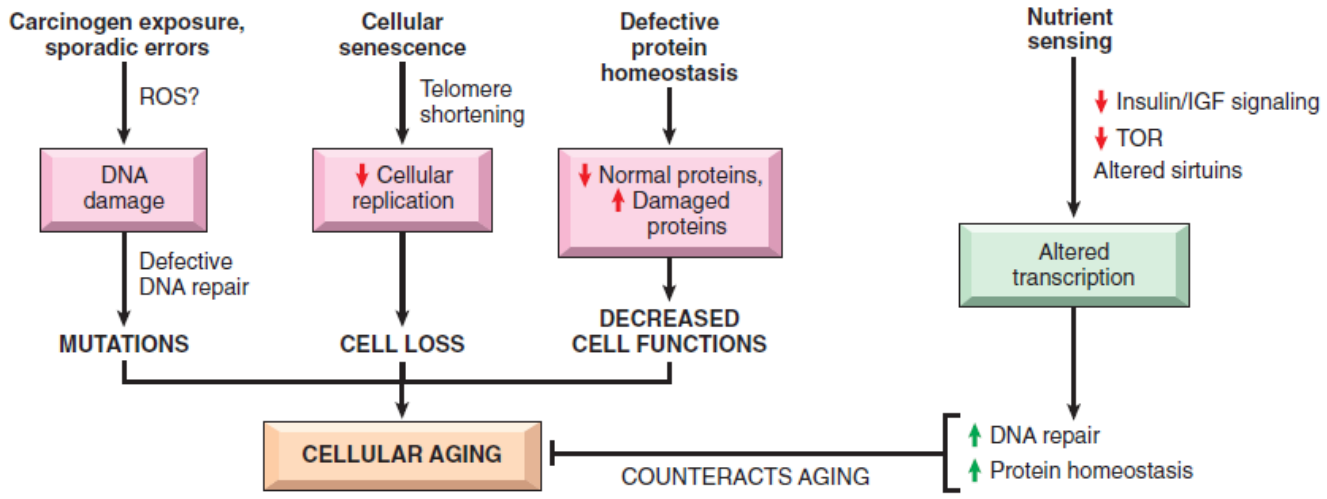


Figure 2.35 Mechanisms that cause and counteract cellular aging. DNA damage, replicative senescence, and decreased and misfolded proteins are among the best described mechanisms of cellular aging. Nutrient sensing, exemplified by caloric restriction, counteracts aging by activating various signaling pathways and transcription factors. *IGF,* Insulin-like growth factor; *ROS,* reactive oxygen species; *TOR,* target of rapamycin.