

exposed to severe nutrient deprivation. Autophagy is also involved in the turnover of organelles like ER, mitochondria, and lysosomes and the clearance of intracellular aggregates that accumulate during aging, stress and various other disease states. Autophagy can trigger cell death if it is inadequate to cope with the stress imposed on the cell. This pathway of cell death is distinct from necrosis and apoptosis, but the mechanism is unknown. Furthermore, it is not clear whether cell death is caused by autophagy or by the stress that triggered autophagy. Nevertheless, autophagic vacuolization often precedes or accompanies cell death.

There is increasing evidence that autophagy plays a role in human diseases. Some examples are listed:

- **Cancer:** This is an area of active investigation and as discussed in Chapter 7, autophagy can both promote cancer growth and act as a defense against cancers.
- **Neurodegenerative disorders:** Many neurodegenerative disorders are associated with dysregulation of autophagy. In Alzheimer disease, formation of autophagosomes is accelerated and in mouse models genetic defects in autophagy accelerate neurodegeneration. In Huntington disease, mutant huntingtin impairs autophagy.
- **Infectious diseases:** Many pathogens are degraded by autophagy; these include mycobacteria, *Shigella* spp., and HSV-1. This is one way by which microbial proteins are digested and delivered to antigen presentation pathways. Macrophage-specific deletion of Atg5 increases susceptibility to tuberculosis.
- **Inflammatory bowel diseases:** Genome-wide association studies have linked both Crohn disease and ulcerative colitis to SNPs in autophagy related genes.

KEY CONCEPTS

Autophagy

- Autophagy involves sequestration of cellular organelles into cytoplasmic autophagic vacuoles (autophagosomes) that fuse with lysosomes and digest the enclosed material.
- Autophagy is an adaptive response that is enhanced during nutrient deprivation, allowing the cell to cannibalize itself to survive.
- Autophagosome formation is regulated by more than a dozen proteins that act in a coordinated and sequential manner.
- Dysregulation of autophagy occurs in many disease states including cancers, inflammatory bowel diseases, and neurodegenerative disorders. Autophagy plays a role in host defense against certain microbes.

Intracellular Accumulations

One of the manifestations of metabolic derangements in cells is the intracellular accumulation of abnormal amounts of various substances that may be harmless or associated with varying degrees of injury. The substance may be

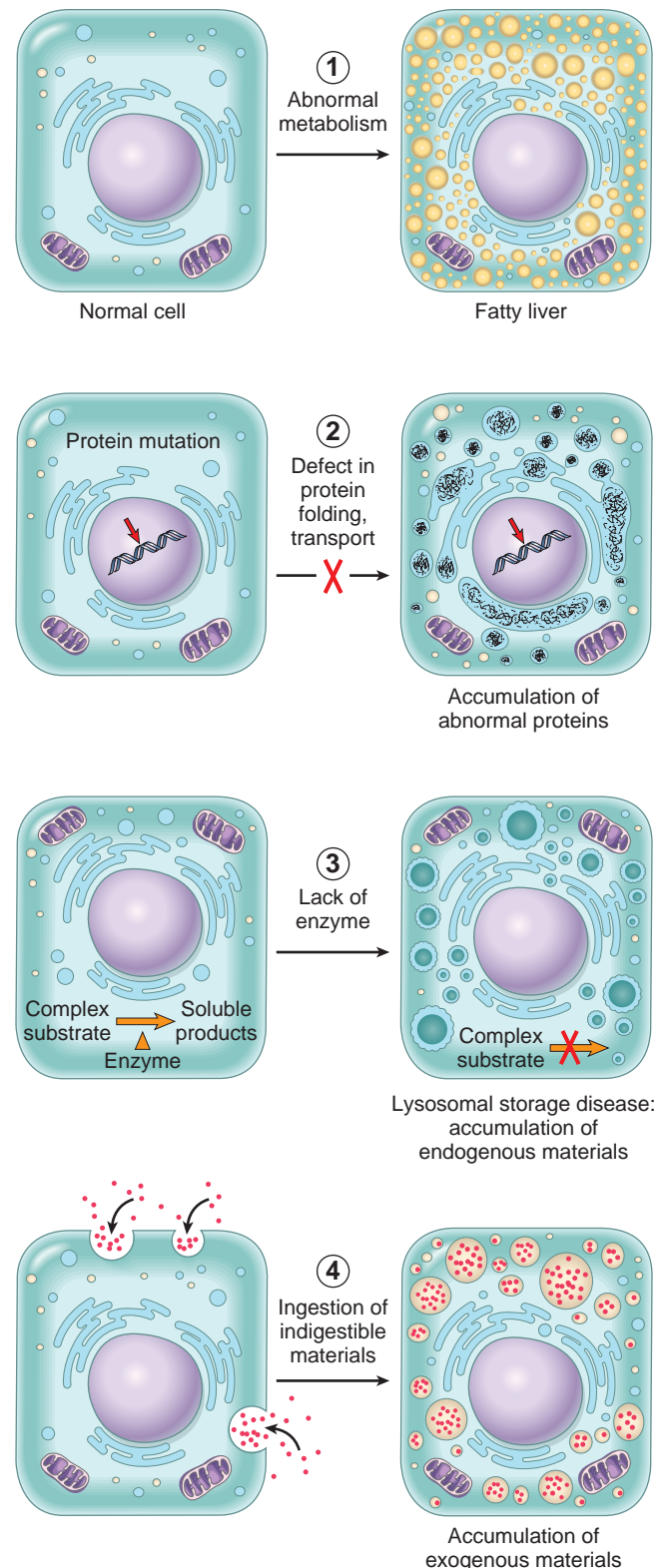


Figure 2-29 Mechanisms of intracellular accumulations discussed in the text.

located in the cytoplasm, within organelles (typically lysosomes), or in the nucleus, and it may be synthesized by the affected cells or may be produced elsewhere.

There are four main pathways of abnormal intracellular accumulations (Fig. 2-29):