KEY CONCEPTS

Necroptosis and Pyroptosis

- Necroptosis resembles necrosis morphologically and apoptosis mechanistically as a form of programmed cell death.
- Necroptosis is triggered by ligation of TNFR1, and viral proteins of RNA and DNA viruses.
- Necroptosis is caspase-independent but dependent on signaling by the RIP1 and RIP3 complex.
- RIP1-RIP3 signaling reduces mitochondrial ATP generation, causes production of ROS, and permeabilizes lysosomal membranes, thereby causing cellular swelling and membrane damage as occurs in necrosis.
- Release of cellular contents evokes an inflammatory reaction as in necrosis.
- Pyroptosis occurs in cells infected by microbes.It involves activation of caspase-1 which cleaves the precursor form of IL-1 to generate biologically active IL-1. Caspase-1 along with closely related caspase-11 also cause death of the infected cell.

Autophagy

Autophagy is a process in which a cell eats its own contents *(Greek:* **auto,** *self;* **phagy,** *eating).* It involves the delivery of cytoplasmic materials to the lysosome for degradation. Depending on how the material is delivered, autophagy can be categorized into three types:

- *Chaperone-mediated* autophagy (direct translocation across the lysosomal membrane by chaperone proteins)
- *Microautophagy* (inward invagination of lysosomal membrane for delivery)
- *Macroautophagy* (hereafter referred to as *autophagy*), the major form of autophagy involving the sequestration and transportation of portions of cytosol in a double-membrane bound autophagic vacuole (autophagosome)

Autophagy is seen in single-celled organisms as well as mammalian cells. It is an evolutionarily conserved survival mechanism whereby, in states of nutrient deprivation, the starved cell lives by cannibalizing itself and recycling the digested contents. Autophagy is implicated in many physiologic states (e.g., aging and exercise) and pathologic processes. It proceeds through several steps (Fig. 2-28):

- Formation of an isolation membrane, also called phagophore, and its nucleation; the isolation membrane is believed to be derived from the ER
- Elongation of the vesicle
- Maturation of the autophagosome, its fusion with lysosomes, and eventual degradation of the contents

In recent years, more than a dozen "autophagy-related genes" called *Atgs* have been identified whose products are required for the creation of the autophagosome. While the details of the process are still not fully understood, its outlines have been defined. In a simple model, environmental cues like starvation or depletion of growth factors activate an initiation complex of four proteins that stimulates the assembly of a nucleation complex. This in turn promotes the nucleation of the autophagosomal membrane. The autophagosomal membrane elongates further, surrounds and captures its cytosolic cargo, and closes to form the autophagosome. The elongation and closure of the autophagosomal membrane requires the coordinated action of several ubiquitin-like conjugation systems, including the microtubule-associated protein light chain 3 (LC3). The synthesis of LC3 is augmented during autophagy and it is therefore a useful marker for identifying cells in which autophagy is occurring. The newly formed autophagosome fuses with endosomes and then finally with lysosomes to form an autophagolysosome. In the terminal step, the inner membrane and enclosed cytosolic cargoes are degraded by lysosomal enzymes. There is some evidence that autophagy is not a random process that engulfs cytosolic contents indiscriminately. Instead, it appears that the loading of cargo into the autophagosome is "selective" and that one of the functions of the LC3 system is to "target" protein aggregates and effete organelles.

Autophagy functions as a survival mechanism under various stress conditions, maintaining the integrity of cells by recycling essential metabolites and clearing cellular debris. It is therefore prominent in atrophic cells, which are

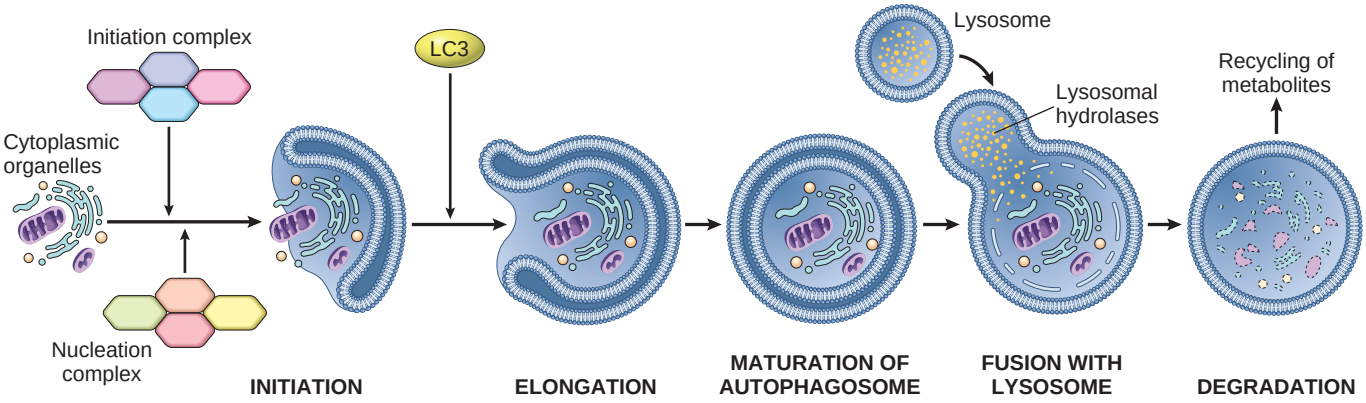

Figure 2-28 Autophagy. Cellular stresses, such as nutrient deprivation, activate an autophagy pathway that proceeds through several phases (initiation, nucleation, and elongation of isolation membrane) and eventually creates double-membrane-bound vacuoles (autophagosome) in which cytoplasmic materials including organelles are sequestered and then degraded following fusion of the vesicles with lysosomes. In the final stage, the digested materials are released for recycling of metabolites. See text for details. (Modified from Choi, AMK, Ryter S, Levine B: Autophagy in human health and disease. N Engl J Med 368:651, 2013.)