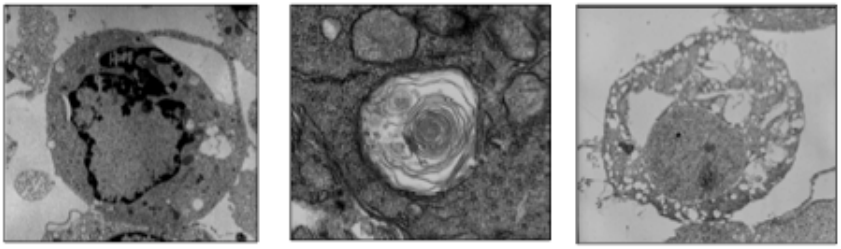
EDITORIAL

Cell death under physiological and pathological conditions occurs with diverse morphological patterns, suggesting highly complex cell death mechanisms (Fig. **1**). Apoptosis is a conserved cell death form essential for normal development and tissue homeostasis in multicellular organisms. Although apoptosis presumably participates in the development of all cell lineages, aberrations in the expression of pro- or anti-apoptotic proteins have been implicated in the initiation of a variety of human diseases, including autoimmunity, immunodeficiency, cancer, neurodegenerative diseases and many others. Several signaling pathways have been implicated in the regulation of apoptosis, including the extrinsic death receptor pathway, and the intrinsic mitochondrial pathway, which depends on activation of cysteine proteases of the caspase family for the execution of apoptosis. In the apoptosis pathway, the BCL-2 family of proteins is located upstream at organelle membranes, controlling the activation of downstream caspases.



Types:	APOPTOSIS	AUTOPHAGY	NECROSIS
Morphology	Cell shrinkage Blebbing. Chromatin condensation DNA degradation Nuclear fragmentation Apoptotic bodies	Decreased cell size Double membrane vesicles Degradation of organelles	Cell swelling Loss of membrane integrity. Organelle swelling. No DNA laddering
Regulators	Death receptors BCL-2 family Caspases, IAPs Adaptor proteins Kinases, phosphatases Calcium, calpains	mTOr, PI3-Kinases ATG family UPR stress sensors Kinases (i.e. JNK) BCL-2 family IP3-receptor	Calcium Ion channels Metabolic failure PARP Calcium-regulated proteins RIP kinases Death receptors Ceramides
Stimuli	Oxidative stress DNA damage Death receptor ligands Developmental programs Organelle stress Anti-cancer drugs Disease mutant proteins ER calcium release	Nutrient starvation Protein aggregation ER stress Calcium overload Developmental programs Hypoxia, ischemia Damaged organelles Proteasome impairment	Bacterial toxins Metabolic poisons Ischemia, stroke Calcium overload

Fig. (1). Characteristic features of cells undergoing apoptosis, necrosis and autophagy.

Although apoptosis is the prevalent form of programmed cell death (PCD) employed to control cell viability and homeostasis during development, increasing evidence indicates that alternative PCD pathways exist that may be particularly relevant under pathological conditions. Necrosis, also referred to as accidental cell death, is characterized by rapid swelling of the dying cell, rupture of the plasma membrane, and release of the cytoplasmic content to the cell environment. Despite the profound effects of necrosis-like cell death in pathological conditions such as stroke, ischemia, and several neurodegenerative diseases, the molecular mechanisms underlying necrotic cell death are poorly understood. Necrosis has traditionally been defined as an unregulated, accidental cell-death process that occurs under conditions of cellular injury related to the loss of ion homeostasis and drastic decreases in ATP levels. In recent years, however, an increasing number of reports indicate that cell death with necrotic features can occur under normal physiological conditions during development by regulated and controlled mechanisms.

Cell death is often associated with the presence of numerous cytoplasmic autophagic vacuoles of lysosomal origin. Lysosomes have been referred to as “suicide bags” because they contain several unspecific digestive enzymes that, upon release into the cytosol, cause autolysis and cell death. Autophagy, also defined as type II PCD, acts as a critical survival response under starvation conditions in which the degradation of intracellular proteins and organe-

lles provides a source of amino acids during poor nutritional conditions. Intracellular components can be delivered to lysosomes for degradation by three different mechanisms known as macroautophagy, microautophagy and chaperone-mediated autophagy. Lysosome-mediated cell death has been linked to the apoptotic pathway through alterations in mitochondrial function, but its actual role as a cell death effecter is actively debated. The hallmark of autophagy is the formation of double-membrane bound autophagosomes. Autophagosomes fuse with lysosomes to form autophagolysosomes, where intracellular components are degraded. Autophagy is a highly regulated process with complex steps controlled by a family of autophagic related genes of the *atg* family which function in diverse processes including development, cell differentiation, tissue remodeling, immunity, host-to-pathogen response and cell death/survival under stress conditions. Members of the BCL-2 protein family have been recently shown to modulate autophagy through the formation of distinct regulatory protein complexes, suggesting a direct link between autophagy and apoptosis.

This special edition of the *Current Molecular Medicine* contains a selection of reviews focused on different aspects of apoptosis, necrosis and autophagy to provide an overview of the relevance of these stress pathways in many physiological and pathological conditions. In this volume of *Curr. Mol. Med.*, Guido Kroemer and María Isabel Colombo give a comprehensive summary of regulatory mechanisms governing autophagy, highlighting its emerging function in both immune response and many intimate connections with cell death. Anthony Letai and Gordon Shore discuss recent data highlighting the relevance of the BCL-2 protein family in disease conditions such as cancer and the possible therapeutic benefits of targeting the pathway with small molecules. To complement this view, Kerstin Reimers describe an uncharacterized family of conserved regulators of cell death, the BAX-inhibitor 1 family, and its possible role in cancer. The inability of a cell to adapt to prolonged perturbations of organelle homeostasis ends with the activation of specific cell death pathways. Accumulation of abnormal protein aggregates composed of misfolded proteins is a common characteristic of many neurological diseases, triggering activation of organelle stress responses. Here we discuss recent data about the involvement of apoptosis and autophagy in neurodegeneration. To complement this view, Dale Bredesen presents a broad view about the role of cell death in neurological disorders. Jean-Claude Martinou and Rosario Rizzuto prepared a deep summary of the involvement of mitochondria in calcium homeostasis and apoptosis, and the relevance of fission/fusion events in cell death and disease conditions. Finally, Andrew Quest, Andres Stutzin and Peter Vandenabeele uncover the molecular regulation of necrosis-like cell death and its role in diverse pathologies. With these set of specialized reviews we aim to provide a comprehensive view of the current understanding of cell death pathways and adaptive reactions to cellular stress. A special emphasis is given on the possible therapeutic benefits of targeting the aforementioned pathways in disease conditions.

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