that are distributed in different cellular compartments and have nonredundant functions designed to adapt bodily functions to various environmental stresses, including food deprivation and DNA damage. Sirtuins are thought to promote the expression of several genes whose products increase longevity. These include proteins that inhibit metabolic activity, reduce apoptosis, stimulate protein folding, and inhibit the harmful effects of oxygen free radicals. Sirtuins also increase insulin sensitivity and glucose metabolism, and may be targets for the treatment of diabetes.

It is thought that caloric restriction increases longevity both by reducing the signaling intensity of the IGF-1 pathway and by increasing sirtuins. Attenuation of IGF-1 signaling leads to lower rates of cell growth and metabolism and possibly reduced cellular damage. This effect can be mimicked by rapamycin. An increase in sirtuins, particularly sirtuin-6, serves dual functions: the sirtuins (1) contribute to metabolic adaptations of caloric restriction and (2) promote genomic integrity by activating DNA repair enzymes through deacylation. Although the antiaging effects of sirtuins have been widely publicized, much remains to be known before sirtuin-activating pills will be available to increase longevity. Nevertheless, optimistic wine-lovers have been delighted to hear that a constituent of red wine may activate sirtuins and thus increase life span!

The various forms of cellular derangements and adaptations described in this chapter cover a wide spectrum, ranging from adaptations in cell size, growth, and function; to the reversible and irreversible forms of acute cell injury; to the regulated type of cell death represented by apoptosis; to the pathologic alterations in cell organelles; to the less ominous forms of intracellular accumulations, including pigmentations. Reference is made to all these alterations throughout this book, because all organ injury and ultimately all clinical disease arise from derangements in cell structure and function.

KEY CONCEPTS

Cellular Aging

- Cellular aging results from a combination of accumulating cellular damage (e.g., by free radicals), reduced capacity to divide (replicative senescence), reduced ability to repair damaged DNA, and defective protein homeostasis
  - **Accumulation of DNA damage:** Defective DNA repair mechanisms; conversely, caloric restriction activates DNA repair and is known to prolong aging in model organisms
  - **Replicative senescence:** Reduced capacity of cells to divide secondary to progressive shortening of chromosomal ends (telomeres)
  - **Defective protein homeostasis:** Resulting from impaired chaperone and proteasome functions.
  - **Nutrient sensing system:** Caloric restriction increases longevity. Mediators may be reduced IGF-1 signaling and increases in sirtuins.

SUGGESTED READINGS

Hypertrophy

Frohlich ED, Susic D: Pressure overload. *Heart Failure Clin* 8:21, 2012. *[A succinct discussion of the pathophysiology of myocardial hypertrophy.]*

van Berlo JH, Maillet M, Molkentin JD: Signaling effectors underlying pathologic growth and remodeling of the heart. *J Clin Invest* 123:37, 2013. *[A review of the cellular and molecular mechanisms of cardiac muscle hypertrophy.]*

Cell Death

Galluzzi L, Kepp O, Trojel-Hansen C, et al: Mitochondrial control of cellular life, stress, and death. *Circ Res* 111:1198, 2012. *[Role of mitochondrial in cellular response to stress.]*

Galluzzi L, Vitale I, Abrams JM, et al: Molecular definitions of cell death subroutines: recommendations of the nomenclature committee on cell death 2012. *Cell Death Differ* 19:107, 2011. *[A summary of molecular definitions of different forms of cell death by an international group of experts.]*

Hausenloy DJ, Yellon DM: Myocardial ischemia-reperfusion injury: a neglected therapeutic target. *J Clin Invest* 123:92, 2013.*[Molecular basis of reperfusion injury and possible therapeutic targets.]*

Nikoletopoulou V, Markaki M, Palikaras K: Crosstalk between apoptosis, necrosis and autophagy. *Biochim Biophys Acta* 2013. *[A general review of different forms of cell death.]*

Apoptosis

Andersen J, Kornbluth S: The Tangled circuitry of metabolism and apoptosis. *Mol Cell* 49:399, 2013. *[A review of the linkage between metabolism and cell death pathways regulated by Bcl-2.]*

Chipuk J, Moldoveanu T, Llambi F, et al: The BCL-2 family reunion. *Mol Cell* 37, 2010. *[Discussion of the role played by BCL-2 family in regulating cell death.]*

Kaufmann T, Strasser A, Jost PJ: Fas death receptor signaling: roles of Bid and XIAP. *Cell Death Differ* 19:42, 2012. *[A discussion of extrinsic apoptosis and its linkages to other forms of cell death.]*

Martinou JC, Youle RJ: Mitochondria in apoptosis: BCL-2 family members and mitochondrial dynamics. *Developmental Cell* 21, 2011. *[A discussion of the molecular mechanisms of intrinsic apoptosis pathway.]*

Necroptosis

Han J, Zhong C, Zhang D: Programmed necrosis: backup to and competitor with apoptosis in the immune system. *Nat Immunol* 12:1143, 2011. *[An excellent discussion of the functional and molecular connection between apoptosis and necroptosis.]*

Kaczmarek A, Vandenabeele P, Krysko DV: Necroptosis: the release of damage-associated molecular patterns and its physiological relevance. *Immunity* 38:209, 2013. *[A discussion of the role of RIP1 and RIP3 in necroptosis.]*

Vanden Berghe T, Linkermann A, Jouan-Lanhouet S, et al: Regulated necrosis: the expanding network of non-apoptotic cell death pathways. *Nat Rev Mol Cell Biol* 15:135, 2014. *[A current review of various forms of programmed non apoptotic pathways of cell death.]*

Autophagy

Choi AMK, Ryter S, Levine B: Autophagy in human health and disease. *N Engl J Med* 368:7, 2013. *[An excellent discussion of the mechanisms and significance of autophagy.]*

Nixon R: The role of autophagy in neurodegenerative disease. *Nat Med* 8:983, 2013. *[An in depth discussion of autophagy and neurodegenerative disorders.]*

Aging

Guarente L: Sirtuins, aging, and medicine. *N Engl J Med* 364:23, 2011. *[The role of sirturins in aging in a clinical context.]*

Lopez-Otin C, Blasco MA, Partridge L, et al: The hallmarks of aging. *Cell* 153:1194, 2013. *[A landmark review that suggest nine hallmarks of aging and directions for future research.]*

Newgard CB, Sharpless NE: Coming of age: molecular drivers of aging and therapeutic opportunities. *J Clin Invest* 3:946, 2013. *[A summary of key molecular pathways in aging.]*