Preface

The aim of *Apoptosis, Cell Signaling, and Human Diseases: Molecular Mechanisms* is to present recent developments in cell survival and apoptotic pathways and their involvement in human diseases, such as cancers and neurodegenerative disorders. This requires an integration of knowledge from several fields of research, including pathology, genetics, virology, cell biology, medicine, immunology, and molecular biology. This edition of the book examines the impact of molecular biology on disease mechanisms. With recent advances in technology such as microarray and proteomics, new biomarkers and molecular targets have been identified. These potential targets will be very useful for the development of novel and more effective drugs for the treatment of human diseases. The challenge now is not only to understand disease mechanisms but also to apply this knowledge to find therapies that are more effective.

Cellular processes play major roles in cell survival and apoptosis. These events are essential for tissue homeostasis and the maintenance of proper growth and development of multicellular organisms. Imbalance in survival and apoptotic pathways may lead to several diseases. Therefore, understanding the molecular mechanisms of cell survival and apoptotic pathways is essential for the treatment and prevention of human diseases. The main focus of *Apoptosis, Cell Signaling, and Human Diseases: Molecular Mechanisms* is to discuss the recent development in cell signaling events, growth, metastasis, and angiogenesis, mechanisms of drug resistance, and targeted therapy for human diseases. Volume 1 contains 15 chapters divided into two sections: "Malignant Transformation and Metastasis" and "Molecular Basis of Disease Therapy"; Volume 2 contains 18 chapters, also divided into two sections: "Kinases and Phosphatases" and "Molecular Basis of Cell Death." Scientists well known in their fields have contributed to this book.

In part I, the pathophysiological processes including the mechanisms by which normal cells are transformed to malignant cells, regulation of cell growth, differentiation and apoptosis by oncogenes and tumor suppressor genes, consequences of DNA damage and the ability of cells to repair damaged DNA in response to stress stimuli, molecular events involved in metastasis and angiogenesis, and roles of transcription factors and cytokines in cell survival and apoptosis, are discussed. The recent development in technology has allowed us to identify new diseases before the appearance of the symptoms. The delay in identification of the disease may be fatal to human life. The incorporation of concepts of engineering to the principles of biology has further revolutionized the field of medicine. Nanotechnology, bioinformatics, microarray and proteomics are powerful tools that are being used in drug discovery and development, and treatment of human diseases.

In part II, biological significance of the kinases, and the cell signaling events that control cell survival and apoptosis are discussed. The identification of over 500 protein kinases encoded by the human genome sequence offers one measure of the

importance of protein kinase networks in cell biology. Phosphorylation and dephosphorylation of protein kinases such as protein kinase A (PKA), protein kinase C (PKC), cyclin-dependent kinase (CDK), phosphatidylinositol 3-kinase (PI3K), Akt, and MAP kinase (MAPK) are important for regulating cell cycle, survival, and apoptosis. High-throughput technologies for inactivating genes are producing an inspiring amount of data on the cellular and organismal effects of reducing the levels of individual protein kinases. Despite these technical advances, our understanding of kinase networks remains imprecise. Major challenges include correctly assigning kinases to particular networks, understanding how they are regulated, and identifying the relevant in vivo substrates. Genetic methods provide a way of addressing these questions, but their application requires understanding the mutations and how they affect protein-protein interacts.

Apoptosis is a genetically controlled process that plays important roles in embryogenesis, metamorphosis, cellular homeostasis, and as a defensive mechanism to remove infected, damaged, or mutated cells. Molecules involved in cell death pathways are potential therapeutic targets in immunologic, neurologic, cancer, infectious, and inflammatory diseases. Although a number of stimuli triggers apoptosis, it is mainly mediated through at least three major pathways that are regulated by (i) the death receptors, (ii) the endoplasmic reticulum (ER), and (iii) the mitochondria. Under certain conditions, these pathways may cross talk to enhance apoptosis. Death receptor pathways are involved in immune-mediated neutralization of activated or autoreactive lymphocytes, virus-infected cells, and tumor cells. Consequently, dysregulation of the death receptor pathway has been implicated in the development of autoimmune diseases, immunodeficiency, and cancer. Increasing evidence indicates that the mitochondrial and ER pathways of apoptosis play a critical role in death receptor-mediated apoptosis. Dysregulation of these pathways may contribute to drug resistance.

A lot of progress has been made in understanding the mechanisms of apoptosis. Mitochondria are critical death regulators of the intrinsic apoptotic pathway in response to DNA damage, growth factor withdrawal, hypoxia, or oncogene deregulation. Activation of the mitochondrial pathway results in disruption of mitochondrial homeostasis, and release of mitochondrial proteins. The release of mitochondrial apoptogenic factors is regulated by the pro- and anti-apoptotic Bcl-2 family proteins, which either induce or prevent the permeabilization of the outer mitochondrial membrane. Activation of the death receptor pathway also links the cell-intrinsic pathway through Bid. Mitochondrial membrane permeabilization induces the release of mitochondrial proteins (e.g., cytochrome c, Smac/DIABLO, AIF, Omi/HtrA2, and endonuclease G), which are regulated by proapoptotic and antiapoptotic proteins of Bcl-2 family, and in caspase-dependent and -independent apoptotic pathways. The antiapoptotic members (e.g. Bcl-2 or Bcl-X_L) inhibit the release of mitochondrial apoptogenic factors whereas the proapoptotic members (e.g. Bax, and Bak) trigger the release.

Recent studies suggest that, in addition to mitochondria and death receptors, other organelles, including the endoplasmic reticulum (ER), Golgi bodies, and lysosomes, are also major points of integration of proapoptotic signaling and damage sensing. Each organelle possesses sensors that detect specific alterations, locally activate signal transduction pathways, and emit signals that ensure inter-organellar cross-talk.

The genomic responses in intracellular organelles, after DNA damage, are controlled and amplified in the cross-signaling via mitochondria; such signals induce apoptosis, autophagy, and other cell death pathways.

Chromatin remodeling agents modulate gene expression in tumor cells. Acetylation and deacetylation are catalyzed by specific enzyme families, histone acetyltransferases (HATs) and deacetylases (HDACs), respectively. Since aberrant acetylation of histone and nonhistone proteins has been linked to malignant diseases, HDAC inhibitors bear great potential as new drugs due to their ability to modulate transcription, induce differentiation and apoptosis, and inhibit angiogenesis. The preclinical data on HDAC inhibitors are very promising, and several HDAC inhibitors are currently under clinical trials for the treatment of cancers.

Apoptosis, Cell Signaling, and Human Diseases: Molecular Mechanisms will be valuable to graduate students, postdoctoral and medical fellows, and scientists with a working knowledge of biology and pathology who desire to learn about the molecular mechanisms of human diseases and therapy. I hope that individuals of diverse backgrounds will find these volumes very useful.

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