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Berek & Hacker's Gynecologic Oncology

FIFTH EDITION

Jonathan S. Berek • Neville F. Hacker

Wolters Kluwer Health | Lippincott Williams & Wilkins

Berek & Hacker's
Gynecologic Oncology

Fifth Edition

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To our wives, Deborah and Estelle; and to our patients whose courage in adversity inspires us to continue our work.

Foreword to the First Edition

Close to the beginning of this century, William Osler observed, "The practice of medicine is an art, based on science." That brief characterization of our profession rings true, even as we approach the next century in the midst of brilliant, accelerating scientific discovery.

Some aspects of the art—including compassion and the basic skills of history taking and physical examination—are, or should be, common to all physicians and remain largely unchanged by a century of research. In other ways, the "art," which can also be translated as "craft" from the original Greek work "techne," has been greatly enlarged and diversified by science and technology. Thus, the special skills required by a gynecologic oncologist derive not only from experience and practice, but also from the proliferation of knowledge in many branches of science. Indeed, it is mainly the developments of science in obstetrics and gynecology—and in some other disciplines—that have evolved the clinical subspeciality of gynecologic oncology.

The art and the science are connected not only by ancestry, however. Their relationship continues to be an interdependent one. One of the ever-expanding glories of medicine is that what is learned in the laboratory can enhance learning at the bedside and what is learned from experience with patients helps to shape and direct scientific inquiry.

Doctors who remain lifelong students are exhilarated by these interconnections and make the best teachers of clinical medicine. It is in the scholarly tradition that Jonathan S. Berek and Neville F. Hacker, with contributions from distinguished colleagues in their own discipline and in fields that bear upon it, have brought together the salient information required to develop the acumen and skills that enable clinicians to understand and to care for women suffering from tumors.

Practical Gynecologic Oncology reflects the indivisibility of art and science in medicine. The two editors—one in Los Angeles and one in Sydney—worked and studied together for 7 years in the same hospital and laboratories and remain mutually helpful intellectual allies on opposites shores of the Pacific Ocean.

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Preface

Gynecologic oncology, as a subspecialty of Obstetrics and Gynecology, evolved slowly since the concept was first introduced in the United States in 1973. Canada, the United Kingdom, Australia, and New Zealand adopted the concept within the ensuing 15 years, and European countries followed later. Although gynecologic oncology was practiced by individuals in Western Europe for many years, official recognition of the subspecialty has been much more recent. Eastern Europe, India, and much of Asia have yet to officially recognize this discipline.

With subspecialization, research into gynecologic cancers flourished at both the clinical and molecular level, and accrual of knowledge expanded exponentially. The development of international collaborative groups like the Gynecologic Cancer Intergroup (GCIG) resulted in the recruitment of large numbers of patients for clinical trials within a relatively short period of time. Similarly, the multinational Human Genome Project paved the way for a better understanding of the genetic basis of cancer and facilitated the development of targeted therapies.

The first four editions of our book were titled *Practical Gynecologic Oncology,* and now, in recognition of its sustained utility, Lippincott Williams & Wilkins has renamed the fifth edition *Berek & Hacker's Gynecologic Oncology*. The previous edition was translated into Chinese and Spanish, an acknowledgment of the book's international appeal.

This edition preserves the basic format and style of the previous editions, being divided into four sections: general principles, disease sites, medical and surgical topics, and quality of life. All chapters have been thoroughly revised and incorporate a critical review of the recent literature. As with previous editions, where level I evidence is not available, we have injected our personal biases, but have tried to justify our position with adequate reference to the available literature. In this edition, a chapter on cancer in pregnancy has been added.

This book would not have been possible without the contributions of our co-authors, who are all acknowledged experts in their field. Dr. Michael Friedlander, an internationally recognized authority on the management of gynecologic cancer, has been recruited as an author. For the past two decades, he has served as the consultant medical oncologist at the Royal Hospital for Women in Sydney, Australia, and his inclusion gives added strength to the chapters on cervical, endometrial, and ovarian cancer. We are most grateful to Tim Hengst and George Barile for their outstanding illustrations and drawings, and to Deborah Berek for her valuable assistance with design and editing. We thank Estelle Hacker for her assistance with the manuscript. We gratefully acknowledge Kerry Garcia for her assistance at Stanford. We appreciate the important contribution of the Lippincott Williams & Wilkins staff, especially Sonya Seigafuse, Nicole Walz, Kerry Barrett, and of Daisy Sosa from Macmillan. Finally, we extend special thanks to Charley Mitchell who has been supportive of our book since its inception.

At Stanford, we acknowledge the generosity of our benefactors, especially Nicole Kidman and the Stanford Women's Cancer Program, as well as the support of our colleagues, Beverly Mitchell, the Director of the Stanford Cancer Center, and Dean Philip Pizzo of the Stanford University School of Medicine. In Sydney, we acknowledge the support of our Gynaecological Oncology (GO) Research Committee, especially Aleco Vrisakis, our Chairman, and Carmen Duncan, our Fund Raising Coordinator. At both institutions, the enduring support of our benefactors has been critical to our gynecologic oncology research and clinical programs.

Our book is written primarily for gynecologic oncologists and fellows undertaking training in gynecologic oncology and consultant gynecologists, as well as medical oncologists and radiation oncologists whose practices involve a significant component of gynecologic cancer care.

We offer this book to those who strive to improve the care of women with gynecologic malignancies.

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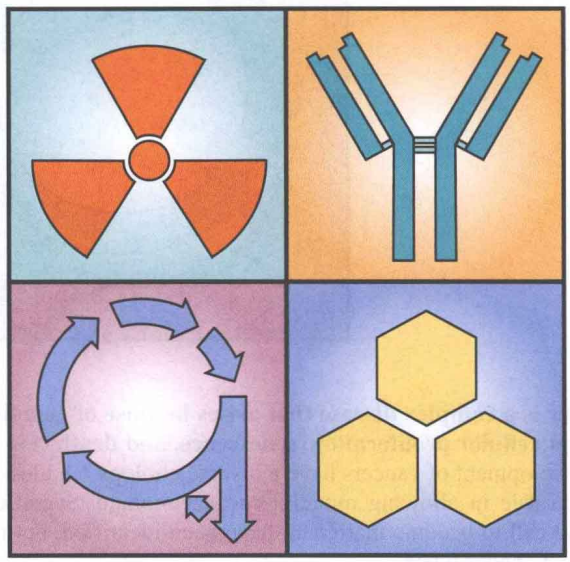
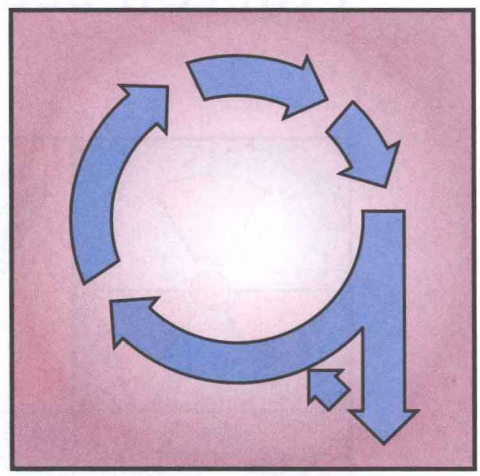
GENERAL PRINCIPLES



1 Biology and Genetics

G. Larry Maxwell
Anil Sood
Andrew Berchuck



Cancer is a complex disease that arises because of genetic and epigenetic alterations that disrupt cellular proliferation, senescence, and death (Fig. 1.1). The alterations that underlie the development of cancers have a diverse etiology, and loss of DNA repair mechanisms often plays a role in allowing mutations to accumulate. Specific molecular changes that cause a normal cell to become malignant have been identified, but their spectrum varies considerably between cancer types.

The malignant phenotype is also characterized by its ability to invade surrounding tissues and metastasize. The development of a cancer elicits a considerable molecular response in the local microenvironment that is characterized by recruitment of stromal elements such as new blood vessels and by an active immunological response. These secondary events play a critical role in the evolution and progression of cancers. Although the molecular pathogenesis of gynecologic cancers has been only partially elucidated, advances in the understanding of these diseases are providing the opportunity for improvements in diagnosis, treatment, and prevention.

The initial sections of this chapter will outline what is known regarding the basic molecular mechanisms involved in the development of cancers and the evolution of the malignant phenotype. The molecular alterations characteristic of gynecologic cancers will be outlined in the latter sections.

Growth Regulation

Proliferation

The number of cells in normal tissues is tightly regulated by a balance between cellular proliferation and death. The final common pathway for cell division involves distinct molecular switches that control cell cycle progression from G_1 to the S phase of DNA synthesis. These include the retinoblastoma (*Rb*) and E2F proteins and their various regulatory cyclins, cyclin-dependent kinases (cdks), and cdk inhibitors. Likewise, the events that facilitate progression from G_2 to mitosis and cell division are regulated by other cyclins and cdks (Fig. 1.2).

In some tissues—such as the bone marrow, epidermis, and gastrointestinal tract—the life span of mature cells is relatively short, and high rates of proliferation by progenitor cells are required to maintain the population. In other tissues—such as liver, muscle, and brain—cells are long lived, and proliferation rarely occurs. Complex molecular mechanisms have evolved to closely

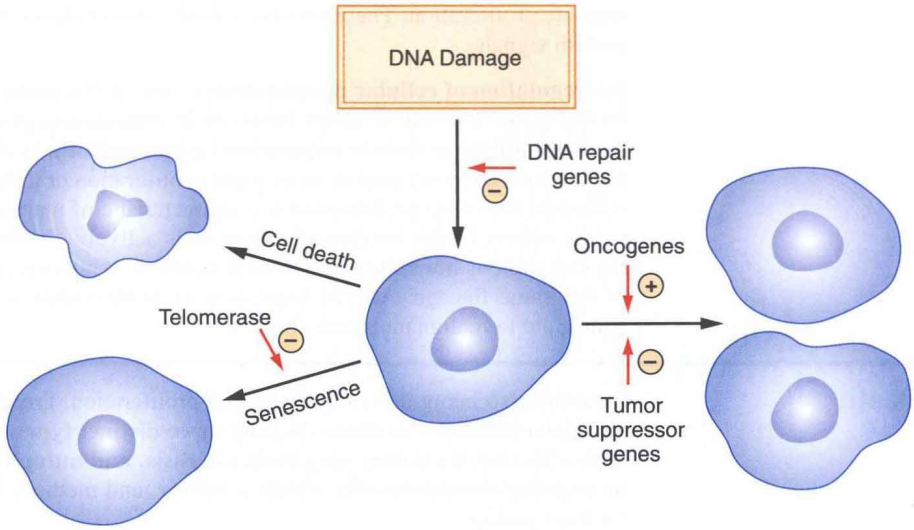


Figure 1.1 **Role of proliferation, cell death, senescence, and DNA damage in cancer development.**

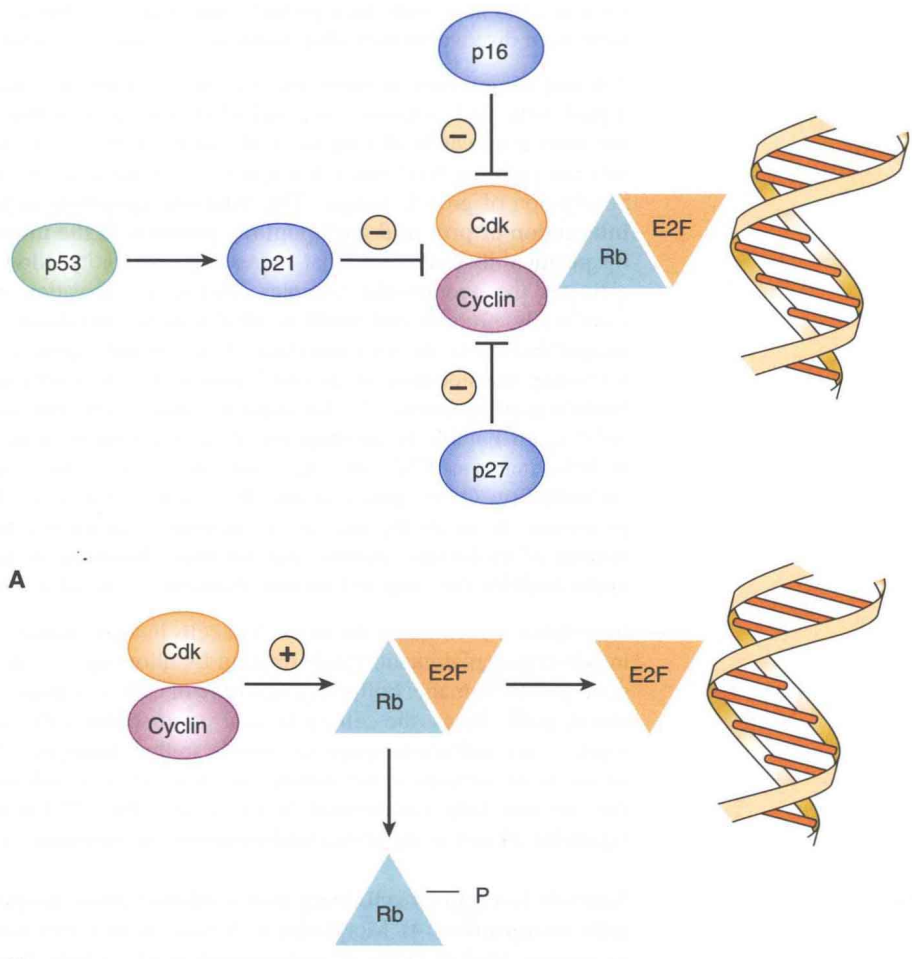


Figure 1.2 **Regulation of cell cycle arrest in G_1 by cyclin-dependent kinase (cdk) inhibitors.** (A) cell cycle arrest (B) cell cycle progression.

regulate proliferation. These involve a finely tuned balance between stimulatory and inhibitory growth signals.

Dysregulation of cellular proliferation is one of the main hallmarks of cancer. There may be increased activity of genes involved in stimulating proliferation (oncogenes) or loss of growth inhibitory (tumor suppressor) genes or both. In the past, it was thought that cancer might arise solely because of more rapid proliferation or a higher fraction of proliferating cells. Although increased proliferation is a characteristic of many cancers and is an appealing therapeutic target (1), the fraction of cancer cells actively dividing and the time required to transit the cell cycle is not strikingly different between many cancers and corresponding normal cells of the same lineage. Altered regulation of proliferation is only one of several factors that contribute to malignant transformation.

Cell Death

In addition to being driven by increased proliferation, growth of a cancer may be attributable to cellular resistance to death. **At least three distinct types of cell death pathways have been characterized, including apoptosis, necrosis, and autophagy** (2). **All three pathways may be ongoing simultaneously within a tumor**, and methods that distinguish between them are far from perfect.

Apoptosis

The term ***apoptosis*** derives from Greek and alludes to a process akin to leaves dying and falling off a tree. Apoptosis is an active, energy-dependent process that involves cleavage of the DNA by endonucleases and proteins by proteases called ***caspases*.** Morphologically, apoptosis is characterized by condensation of chromatin, nuclear and cytoplasmic blebbing, and cellular shrinkage. The molecular events that affect apoptosis in response to various stimuli are complex and have only been partially elucidated (3), but several reliable markers of apoptosis have been discovered including annexin V, caspase-3 activation, and DNA fragmentation (4).

External stimuli such as tumor necrosis factor, tumor necrosis factor-related apoptosis-inducing ligand, fatty acid synthase (Fas), and other death ligands that interact with cell surface receptors can induce activation of caspases and lead to apoptosis via an extrinsic pathway (Fig. 1.3). The intrinsic pathway is activated in response to a wide range of stresses including DNA damage and deprivation of growth factors. **The intrinsic apoptosis pathway is regulated by a complex interaction of pro- and antiapoptotic proteins in the mitochondrial membrane that affect its permeability.** Proteins that increase permeability allow release of cytochrome c, which activates the apoptosome complex leading to activation of caspases that affect apoptosis. Conversely, proteins that stabilize mitochondrial membranes inhibit apoptosis. The first major insight that led to the understanding of the intrinsic apoptosis pathway was the finding that an activating translocation of the *bcl-2* gene in B-cell lymphomas results in essentially complete inhibition of apoptosis (5). Subsequent studies demonstrated that the antiapoptotic effect of *bcl-2* is attributable to stabilization of the mitochondrial membrane. Additional genes related to *bcl-2* (such as *BAD, BCL-XL,* and others) also block apoptosis by inhibiting membrane permeability. Other genes in the *BCL* family (such as *BAX, BAK,* and others) increase membrane permeability and are proapoptotic. **An increased understanding of the complex system of molecular checks and balances involved in regulation of apoptosis provides opportunities for targeted cancer therapies;** several strategies are under development (6).

In addition to restraining the number of cells in a population, apoptosis serves an important role in preventing malignant transformation by allowing the elimination of cells that have undergone genetic damage. Following exposure of cells to mutagenic stimuli, including radiation and carcinogenic drugs, the cell cycle is arrested so that DNA damage may be repaired. If DNA repair is not sufficient, apoptosis occurs so that damaged cells do not survive (Fig. 1.1). This serves as an anticancer surveillance mechanism by which mutated cells are eliminated before they become fully transformed. In this regard, **the *TP53* tumor suppressor gene is a critical regulator of cell cycle arrest and apoptosis in response to DNA damage.**

Necrosis

Necrosis is a type of cell death that is distinct from apoptosis and is the result of bioenergetic compromise (4). Morphologic changes include swollen organelles and rupture of the cell membrane, leading to loss of osmoregulation and cellular fragmentation. **Necrosis is a less well regulated process that leads to spillage of protein contents, and this may incite a brisk immune response.** This is in contrast to the silent elimination of cells by apoptosis, which typically elicits a minimal immune response. There is evidence that some drugs may enhance necrotic death in tumors, and this may stimulate a beneficial antitumor immune response.

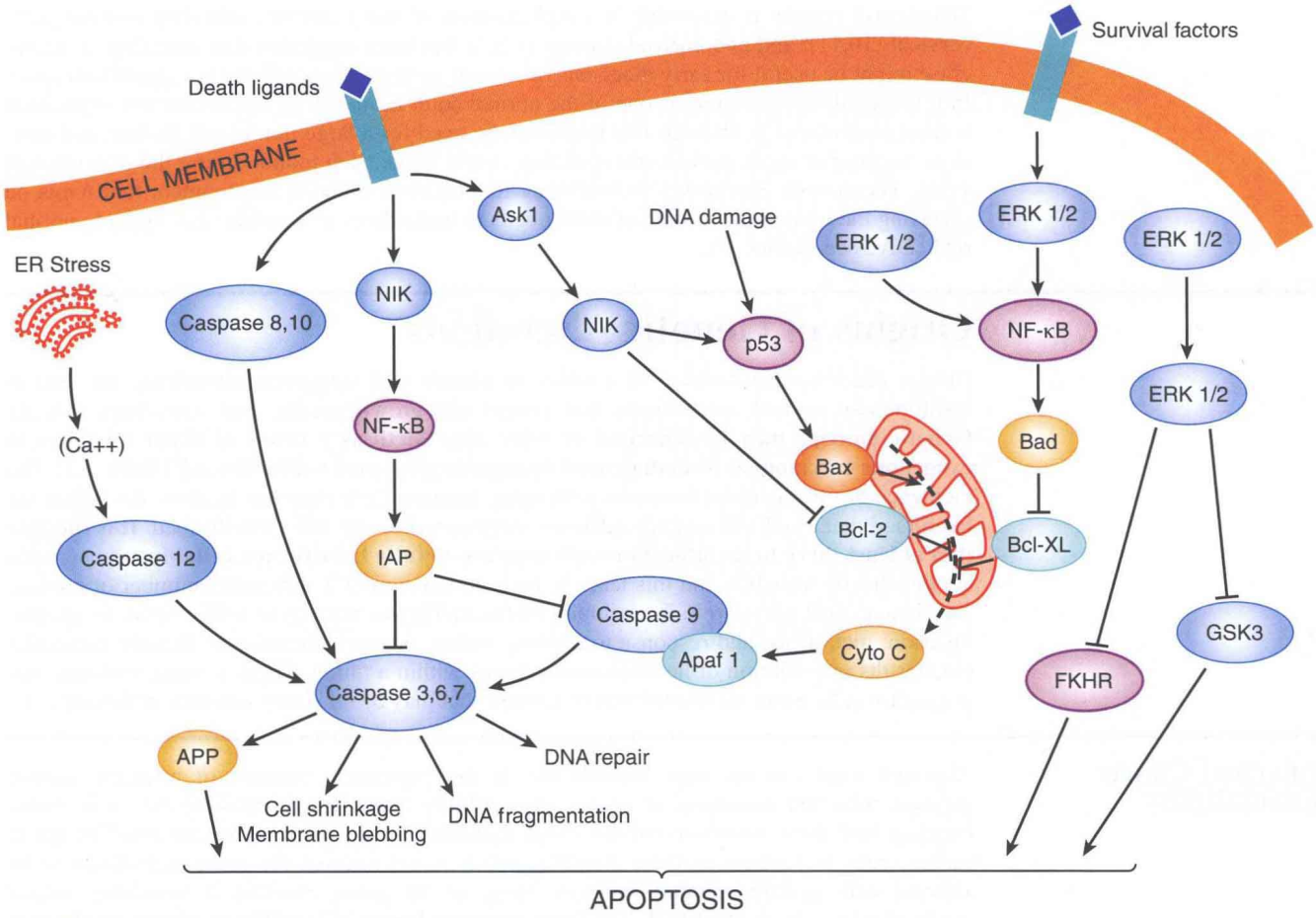


Figure 1.3 **Apoptosis pathways.**

Autophagy

Autophagy is a potentially reversible process in which a cell that is stressed "eats" itself (4). A wide range of stresses have been identified that may elicit autophagy (some of which may also elicit apoptosis), including growth factor deprivation and accumulation of reactive oxygen species. Unlike necrosis and apoptosis—in which loss of integrity of the cytoplasmic and nuclear membranes, respectively, are defining events—**autophagy is characterized by the formation of cytoplasmic autophagic vesicles into which cellular proteins and organelles are sequestered.** This may allow for cell survival if damaged organelles can be repaired. Conversely, the process may lead to cell death if these vesicles fuse with lysosomes with resultant degradation of their contents. Several cancer therapeutic agents have been shown to induce autophagy, while targeted disruption of genes such as *ATG5* that are involved in autophagy can inhibit cell death (4).

Cellular Senescence

Normal cells are only capable of undergoing division a finite number of times before becoming senescent. Cellular senescence is regulated by a biological clock related to progressive shortening of repetitive DNA sequences (TTAGGG) called **telomeres** that cap the ends of each chromosome. Telomeres are thought to be involved in chromosomal stabilization and in preventing recombination during mitosis. At birth, chromosomes have long telomeric sequences (150,000 bases) that become progressively shorter by 50 to 200 bases each time a cell divides. **Telomeric shortening is the molecular clock that triggers senescence** (Fig. 1.1). Malignant cells often avoid senescence by turning on expression of telomerase activity to prevent telomeric shortening (7). Telomerase is a ribonucleoprotein complex, and both the protein and RNA subunits have been identified. The RNA component serves as a template for telomeric extension, and the protein subunit catalyzes the synthesis of new telomeric repeats.