

Preface

RESEARCH CARRIED OUT OVER THE LAST THREE DECADES OF the 20th century resulted in the identification of oncogenes, tumor-suppressor genes, and genes involved in DNA repair processes as the etiological agents of human cancers. These genes were discovered by studies employing tumor viruses, epidemiological approaches, cloning of genes from the germ lines of patients with cancer predisposition syndromes, and analysis of the genomes of tumors. The first decade and a half of the 21st century resulted in the collection of large numbers of genomic sequences from a wide variety of tumor types and normal tissues of patients, which demonstrated the presence of mutations in a number of these oncogenes, tumor-suppressor genes, and DNA repair genes in selected tumor types. The frequency with which these genes are mutated in human cancers varies with the tumor tissue type, age of the patient, and presence of an inherited predisposition to develop cancer. The contribution of these diverse gene mutations to the origin of all types of human cancers can be roughly divided into three categories: Some genes are observed to be mutated at a frequency of 1%–5%, a smaller set of genes is altered at a frequency of 30%–40%, and one gene, the gene that encodes p53, is mutated in more than half of all human cancers combined.

Many of the mutated genes in the 1%–5% group encode receptor protein kinases or protein kinases, and most drugs developed by the pharmaceutical companies inhibit these targets. They can have diverse patterns of mutation frequency in different tumor types. For example, B-RAF mutations are found at ~50% frequency in melanomas but have a 5%–7% frequency in colon and other cancers. The 30%–40% category includes RAS, PI 3-kinase, BCL-2, and MYC, which have been difficult to develop drugs against (only a γ/δ PI 3-kinase drug is approved at this time) but are an important set of genes whose functions are under intensive study.

More than 50% of all human cancers (greater than 22 million people worldwide are alive today with cancers) have somatic p53 mutations (see the chapter by Hainaut and Pfeifer), and the frequency of this mutation varies depending on the cell or tissue type. One hundred percent of serous ovarian cancers have p53 mutations, whereas only 1%–2% of testicular teratocarcinomas harbor p53 mutations. High levels of expression of several oncogenes (see the chapters by Wasylshen and Lozano, Oliner et al., and Marine and Jochemsen), such as MDM2 or MDM4, can inactivate the wild-type p53 functions, and genetic modifiers can alter the p53 pathway, reducing or changing its functions in cancers (see the chapter by Basu and Murphy). Inherited mutations in the p53 gene commonly result in early-onset cancers with an increased risk of threefold to 1000-fold greater frequencies, depending on the age of the patient and tumor tissue type (see the chapters by Levine et al., Achatz and Zambetti, Shetzer et al., and Guha and Malkin). Based on these observations it is clear that the p53 gene and its protein play a central role in the prevention and causes of cancers. If we are to understand the origins, treatment, and development of cancers in humans, both the basic and clinical functions of the p53 protein in normal and cancerous tissues must be elucidated (see the chapter by Aylon and Oren). That is the purpose and goal of this volume.

Six years ago, Cold Spring Harbor Laboratory Press published a volume entitled *The p53 Family*, which largely focused on the basic science of the p53 protein and its relatives, the p63 and p73 family of transcription factors. Over the past 6 years, the field has begun to change its focus by studying the role of the p53 protein using clinical material from patients. To reflect this change in direction, this volume is divided into four parts.

- I. *The Structure and Functions of the p53 Protein*. This section (chapters by Aylon and Oren, Chillemi et al., Jorruiz and Bourdon, Raj and Attardi, Pfister and Prives, and Aubrey et al.) elucidates and updates new and fundamental observations made over the past few years.
- II. *The Regulation of Cellular Functions by the p53 Protein*. This section reviews all of the cellular functions that contribute to cancer prevention and tumor suppression (as introduced in Sec. I in the chapter by Aubrey et al.). These wide-ranging functions include DNA damage repair (in the chapter by Williams and Schumacher), genomic instability (in the chapter by Eischen), cell cycle arrest and apoptosis (in the chapter by Chen), telomere length regulation (in the chapter by Roake and Artandi), cellular senescence (in the chapter by Tonnessen-Murray et al.), autophagy (in the chapter by White), the regulation of ribosomal biogenesis (in the chapter by Deisenroth et al.), the regulation of cellular metabolism and hypoxia (in the chapter by Humpton and Vousden), the role of p53 in stem cell function and epigenetic fates (in the chapter by Levine et al.), and the role of p53 in inflammation (in the chapter by Gudkov and Komarova).
- III. *p53 Mutations in Human Cancers*. In this section, chapters by Hainaut and Pfeifer, Achatz and Zambetti, Shetzer et al., Wasylishen and Lozano, and Guha and Malkin compare and contrast the inherited and somatic mutations in the p53 gene and other genes that compromise p53 function leading to cancers. The impact of mutant p53 proteins on tumor development and growth, thought to be a gain of function, is reviewed in chapters by Aylon and Oren (Sec. I) and by Shetzer et al., and the clinical outcomes of p53 mutations are explored in the chapter by Robles et al. (Sec. IV).
- IV. *The p53 Pathway in Human Cancers—Clinical Manifestations*. The final section deals with the modifiers of the p53 pathway (in the chapter by Basu and Murphy), the role of mutations in p53 and other genes in specific types of tumors (in the chapters by Oliner et al., Marine and Jochemsen, Silwal-Pandit et al., Ablain et al., Ramaswamy et al., Comeaux and Mullighan, and Robles et al.), and the drugs developed to respond to these tumors (in the chapters by Wang et al. and by Cheok and Lane). This progression of chapters accurately reflects the movement of p53-related research into the clinic and a new understanding of p53 functions in humans.

In the second section, 10 functions of the p53 protein are reviewed, each of which responds to different stress signals (via the MDM-2/MDM-4 complex) and prevents pathogenic outcomes. In the aggregate, this enforces tumor suppression in an organism (see the chapter by Aubrey et al. in Sec. I). Each type of stress signal triggers a p53-mediated transcriptional response that sets off diverse signal transduction pathways to produce its outcome. It has become clear that both the stress signals that p53 responds to and the resultant transcriptionally activated p53 protein function differently in different cell and tissue types. The p53 pathway and its regulation are distinct in different tissues of the body. At this time we do not know a great deal about tissue-specific p53 stress responses and transcriptional outcomes in the human. Undoubtedly this is reflected in the heterogeneous distribution of the frequency of p53 mutations in different cancerous tissue types (see the chapter by Hainaut and Pfeifer in Sec. III) and the role of MDM-2 and MDM-4 overexpression and gene amplification in a tissue-restricted fashion (see the chapters by Wasylishen and Lozano, Oliner et al., and Marine and Jochemsen). This tissue-specific heterogeneity is also reflected in patients with inherited p53 mutations (see the chapters by Levine et al., Achatz and Zambetti, Wasylishen and Lozano, and Guha and Malkin). The role of p53 (and MDM-2) in stem cells, tissue regeneration, and epigenetic alterations in cells provides a guide to the possible roles of mutant p53 in cancers and cancer stem cells (see the chapters by Aylon and Oren, Levine et al., and Guha and Malkin). An in-depth understanding of normal p53 functions will surely improve our understanding of developmental diseases (see the chapters by Deisenroth et al., Gudkov and

Komarova, and Ablain et al.), inflammatory processes, immunity (see the chapter by Gudkov and Komarova), and longevity.

This volume is meant to bring together research scientists and students in basic, translational, and clinical research. The editors have invited experts in these diverse areas to inform those who want to enter the field and to provide a long list of questions that are important and not yet answered. We hope to entice the next generation of basic scientists and clinicians to focus their efforts to understand cancer biology and the unique role that the p53 gene and its protein play in the origins, development, and treatment of this disease.

We are grateful to Richard Sever at Cold Spring Harbor Laboratory Press for his vision in suggesting a second p53 volume based on the rapid progress made and the shift in the direction of the field into clinical research, which we wanted to bring to the community of scholars. We also extend our sincere thanks to Barbara Acosta at Cold Spring Harbor Laboratory Press for her constant help in communicating with both the authors and the editors, always keeping the project on target and constantly working to keep the project on time. We are indebted to each of the authors for taking time out to write their chapters. They have stimulated the field and invited many others to join us in this ever-expanding universe that has become the p53 field.

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