

Preface

Every day, mammalian cells accumulate an estimated 100,000 lesions in their DNA resulting from exposure to reactive oxygen species, chemical deterioration of their bases, and exposure to exogenous agents such as ultraviolet and ionizing radiation. Cells have evolved complex response mechanisms to recognize and repair this injury in order to maintain genomic integrity in the face of this unrelenting assault. The study of DNA damage response has a long and storied history beginning in the 1940s by scientists like Albert Kelner and Renato Dulbecco. Their work revealed the existence of enzymatic photoreactivation and ultimately laid the foundation for the idea that cells respond to DNA damage and that DNA damage repair does exist. Since that time and with the development of sophisticated molecular techniques, an evolving story regarding the cellular response to DNA injury and its importance has emerged. The spectrum of diseases that have benefited from this contemporary research effort is broad and includes virtually all fields where genotoxic stress from oxidative injury, radiation insult, and chemical exposure plays a role in disease initiation, evolution, and treatment. One of the most important areas where these modern studies have had an impact is in the area of cancer biology. Through these studies, we now have a firmer grasp on the molecular response of the cell to DNA injury and how these responses influence mutagenesis, cell cycle progression, DNA damage signaling, neoplastic transformation, and cancer therapy. This book reviews a number of these important topics and will serve to provide a review of key basic and translational aspects of each.

We have divided the book into two general categories for the purpose of organization: (1) Molecular Basis of DNA Damage Responses, and (2) Modulation of Radiation Responses – Opportunities for Therapeutic Exploitation. In the first section, Dr. Redon and colleagues provide a review of the histone variant, H2AX, and the role of this protein in the early response of the cell to DNA injury. Dr. Bunz discusses key proteins involved in ATM-dependent signaling of DNA injury and the importance of this protein in controlling DNA damage repair. Similarly, Dr. Lobrich, and colleagues discuss the role of signaling molecules and regulators of a complex signaling system that modulates cellular progression through the cell cycle following radiation injury and the link to repair of DNA damage. Drs. Shen and Falbo provide an overview on the critical role of chromatin structure and

proteins associated with chromatin remodeling in the response of the cell to DNA damage and in the maintenance of DNA fidelity. Finally, one of the most versatile model systems that has served to elucidate specific DNA damage response pathways at the organismal level is *Caenorhabditis elegans*. Data derived from this model have been key to our understanding of data generated in higher organisms, including mammalian cells. In their chapter, Drs. Bailly and Gartner review important data on DNA damage signaling, repair, and cell fate generated using this model system.

The book then transitions into a discussion of DNA damage response topics that have therapeutic relevance. First, Dr. Hammond and her colleagues discuss cellular and tumor hypoxia, a critically important microenvironmental condition of many human tumors. They review the molecular underpinnings of the hypoxic state, and how these factors alter radiation-induced DNA injury and repair. Collectively, the chapters by Drs. Vischioni, et al., Freytag, et al., Yazlovitskaya and Hallahan, and Dunn, et al., provide in-depth analyses of molecularly based therapies directed toward a variety of cellular targets, all of which have potential to modulate the response of the cell to radiation-induced DNA damage for therapeutic benefit. This includes discussions on (1) inhibitors of specific proteins known to be involved in DNA strand break repair; (2) development of viral and nonviral gene therapy systems that enhance radiation injury through a variety of DNA-directed mechanisms; (3) identification of pro-survival proteins, induced by radiation in tumor vasculature that can serve as molecular targets for radiation-modifying drugs; and (4) the potential for anti-EGFR agents in combination with radiation to substantially improve the therapeutic benefit of radiation therapy. Next, Dr. Roti Roti, et al., provide a comprehensive review of heat effects on signaling proteins, nuclear matrix-associated proteins and chromatin remodeling, and demonstrate how these heat-induced effects result in substantial alterations in cellular response to radiation. Finally, Dr. Drake reviews the evolving knowledge on the immunological effects of radiation, an area of investigation that has great potential to change the future of cancer care.

Together, these chapters are a collection of contemporary works on DNA injury and the cellular response associated with it. While not every topic in the DNA damage response domain could be reviewed in a monograph of this size, we do believe the authors have done an outstanding job in providing timely and relevant discussions on their respective subjects, allowing the reader to become more familiar with the field and where the future lies within it. We firmly believe the information contained in this book underscores the significance of DNA damage response in cancer research and the need for continued investigation in this area in order to make substantive progress toward eliminating the suffering associated with cancer. We would fully concur with the opinion expressed by Dr. Bruce Alberts when he said: "If I were the czar of cancer research, I would give a higher priority to recruiting more of our best young scientists to decipher the detailed mechanisms of both apoptosis and DNA repair, and I would give them the resources to do so" (ref: Alberts, B, *Science*, 320:19, 2008). We hope that his sentiment and this book will

provide inspiration to those young scientists seeking to work in an area with great potential and importance for our collective future.

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