

Preface

Genome dynamics and stability are the *non plus ultra* requirements for cellular life. No matter whether life began with metabolism, with self-replicating genetic molecules, or as a cooperative chemical phenomenon, all cells and viruses maintain a genome capable of multiplication, variation and heredity. A population of living entities with these properties will evolve by natural selection, and while modern metabolism supplies the monomers from which genomes (i.e. replicators) are made, genomes alter the kinds of chemical reactions occurring in metabolism (Maynard Smith and Szathmary 1997). This book deals with DNA repair and replication. Together with two other planned volumes, one on transposable elements and genome dynamics and another on recombination and meiosis as a key issue of the metazoan germline development, this volume introduces the conceptual framework of the series.

An earlier review on the classic monograph *Mobile DNA* (Berg and Howe 1989) was entitled "On the Impossibility of Knowing More." It states: "This big book indeed tells us everything but says nothing. It provides no conceptual framework as to what the burgeoning bulk of molecular data means, not out of intent but because it is swept along by an attitude found increasingly in science of 'never mind the quality, feel the width' ... the book is essentially uninformative regarding the biological importance of transposable elements in ontogeny and phylogeny" (Dover 1990). The present book series tries to circumvent such criticism. Of course, there have been milder opinions of the monumental *Mobile DNA* book as well (Brookfield 1989; Fincham 1989). Actually, the 2002 publication of its successor *Mobile DNA II* (Craig et al. 2002) impressively demonstrates the swift progress in this significant research field, which now not only largely addresses questions of evolutionary relevance but pragmatically feeds additional knowledge applied in human gene therapy or helps to understand the somatic maturation of the immune system by V(D)J recombination. The latter actually demonstrates the closeness of transposable element transposition to DNA repair as the V(D)J recombination reaction is completed by the non-homologous end joining (NHEJ) DNA repair pathway in lymphocyte development where the DNA double-strand break (DSB) is generated through the transposase (i.e. endonuclease) activity of an ancient transposable element. This transposon inserted into an ancestral vertebrate genome some 450 million years ago (Yu et al. 1999). In line with this important

interface between a vertebrate transposon and DSB repair, the second chapter of Part II of this book reports on a similar relationship of the *Drosophila* P elements triggering DSBs and facilitating the understanding of the mechanisms of replication-dependent DSB repair. Other molecularly fossilized but experimentally revitalized transposable elements which promise to be of biomedical relevance are planned for an upcoming book volume. As Carl Woese recently said, it seems to be about time that biology makes a choice between the comfortable path of continuing to follow molecular biology's lead or the more refreshing one seeking a new and inspiring vision of the living world (Woese 2004).

To accomplish this is my goal with the book series *Genome Dynamics and Stability*, where this first volume is dedicated to integrative aspects of replication and DNA repair providing an overview of some facets and perspectives of genome integrity. DNA integrity is relevant for all organisms, and therefore it opens avenues of curiosity ranging from viroids in applied plant research to grasping biodiversity. This vision however must include pragmatic aspects of biomedical relevance as well.

The book at hand is entitled *Genome Integrity: Facets and Perspectives*. It contains a rather broad spectrum of chapters representing key aspects of DNA repair with a slight bias towards DSB repair as justified by its importance. Actually, every chapter is self-sufficient and could serve as an independent entry point to the whole book. The sequence chosen starts with three chapters introducing replication as a fundamental aspect of life. Here, the first chapter gives a general introduction to replication worth to be read by undergraduate students as well as academics, while the second chapter attempts to present a concept towards an anatomy of the eukaryotic replication fork. The third chapter adds the aspect of human diseases to the two more fundamental aspects in Part I. Replication is then linked by two interface-chapters in Part II to the world of DSB repair. The second chapter of Part II first reviews the history of the discovery of the physical nature of the gene and gene mutations. Exploiting gene targeting as an experimental, technical pillar, it attempts to compose the different models of DSB repair into a unifying synthesis. This joins Part II with four key aspects of DSB repair representing Part III. These four key aspects review the structure and function of the Rad50/SMC protein complexes in chromosome biology, further focus on the simplest pathway for DSB repair, i.e. non-homologous endjoining (NHEJ), and focus on a central gatekeeper crucial to avoiding cancer development, i.e. p53, and the most complex role of chromatin in DSB repair. The chapter on DNA base damage recognition in Part IV introduces DNA repair pathways involving one-strand lesions and their pleiotropic interactions with cell physiological functions, such as cell cycle, apoptosis and examples of major human diseases. While DSBs can be triggered and their repair can be studied at precisely defined positions on nucleotide level within a given chromosome, DNA damage introduced through radiation and other genotoxic stress factors follows a slightly different research lead. This

is the common theme of the four chapters in Part IV. Ion irradiation as a tool to reveal tracts of damage throughout the eukaryote nucleus reminds us of cloud or Wilson chamber experiments in atomic physics detecting elementary particles of ionizing radiation. Here, in the final chapter of Part V, the tract of damage in a cloud of chromatin is monitored using antibodies to proteins characteristic of specific DNA repair pathways, as discussed in the last chapter of Part III. The four final chapters are important for many reasons, ranging from a significance for irradiation treated cancer patients, or victims of the Chernobyl disaster to the exposure to cosmic radiation of astronauts on long-term space missions.

First of all I am very grateful to all contributors for their dedication and trust to participate in the first volume of this new book series. The original idea for this book came from the 8th meeting of the DNA Repair Network in Ulm, Germany, and would not have been possible without the support of the Deutsche Gesellschaft für DNA-Reparaturforschung (DGDR). Here I would like to mention especially Jürgen Thomale, Alexander Bürkle, Lisa Wiesmüller, Bernd Kaina and Friederike Eckardt-Schupp, who supported the initial idea and acted in the background. Further I would like to thank the anonymous referees for doing a great job in peer reviewing and improving the manuscripts. I also thank the University of Heidelberg, which gave access to their electronic journal collection. Last but not least, I have to thank Sabine Schreck (Springer, Heidelberg) without whom I could never have engaged in this project. Ursula Gramm (Springer, Heidelberg) and Michael Reinfarth (LE-TeX GbR, Leipzig) did a fine job copy editing all manuscripts and the Springer team succeeded well in establishing the SpringerLink OnlineFirst version of this book series, which provides authors with more flexibility in the individual handling of their contributions.

References

- Beatty DE, Howe MM (eds) (1989) *Mobile DNA*. American Society for Microbiology, Washington
- Brookfield JFY (1989) Sorting out the 'junk'. *Trends Biochem Sci* 14:428–429
- Craig NL, Craigie R, Gellert M, Lambowitz AM (eds) (2002) *Mobile DNA II*. ASM Press, Washington
- Dover G (1990) On the Impossibility of Knowing More. *Cell* 60:703–704
- Fincham JRS (1989) DNA in flux. *Nature* 342:26–27
- Maynard Smith J, Szathmary E (1997) *The major transitions in evolution*. Oxford University Press, Oxford, New York, Tokyo
- Woese CR (2004) A new biology for a new century. *Microbiol Mol Biol Rev* 68:173–186
- Yu W et al. (1999) Coordinate Regulation of RAG1 and RAG2 by Cell Type-Specific DNA Elements 5' of RAG2. *Science* 285:1080–1084