DNA Replication and Human Disease

Edited by Melvin L. DePamphilis

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Carol S. Newlon

Progress in the field of DNA replication has been astounding in the ten years since publication of the first edition of *DNA Replication in Eukaryotic Cells* in 1996. A second edition of this volume, titled *DNA Replication and Human Disease,* attempts to present a synthesis that conveys the similarities in genome duplication across species and its relationship to cell growth and division in eukaryotes ranging from single-celled organisms (such as yeast and *Tetrahymena*) to multicellular eukaryotes (such as flies, frogs and mammals). With thirty-six chapters, two appendices and seventy-six authors, production of this monograph brought together many leading investigators in the field to write about their specialties. The large number of contributors is both a strength and a weakness of this volume: its strength lies in the completeness of coverage and level of expertise provided by the authors, and the weakness results from a fragmented discussion of many topics and the unevenness of the writing.

The first section of the book, Cellular DNA Replication, begins with an excellent overview of genome duplication by Thomas J. Kelly and Bruce Stillman, followed by chapters on specific steps in the process — including replication origin structure, pre-replicative complex assembly and activation, proteins at the replication fork and replication termination. These chapters, coauthored by individuals with expertise in yeast and metazoan systems, provide a synthesis of findings from both systems. This section also provides chapters on other aspects of genome duplication, including chromatin assembly, perpetuation of genome methylation patterns, the inter-relationship between DNA replication and nuclear structure, and the temporal order of replication. A topic conspicuously missing from this section is establishment of sister chromatid cohesion.

The second section focuses on regulation of DNA replication and cell proliferation. The two chapters on regulating replication initiation events in yeasts and in metazoa are nicely done, but they suffer from being separated from the chapters in the previous section on pre-replicative complex assembly and activation. Although there is little redundancy, the reader is forced to refer back and forth between the sections to obtain a picture of how the events fit together. The other two chapters in this section cover responses to abnormal DNA replication and DNA damage during S phase. Our understanding of these checkpoint signal transduction pathways was in its infancy when the first edition of this monograph was published, and the authors of these two chapters do an outstanding job of summarizing our current, incomplete, understanding of these important regulatory systems. It seems likely that the next ten years will see the development of unifying concepts that connect what now seem to be disparities between the systems that have been examined, and the clarification of both the upstream sensors and the downstream targets of these pathways — which remain poorly understood.

The third section focuses on the relationship between cellular DNA replication proteins and human disease. There are important, often unappreciated, connections here. In his preface, DePamphilis points out that 40 human diseases are caused by mutations in genes required for DNA replication or repair, another 7 are caused by mutations generated during mitochondrial DNA replication, and 38 result from expansion or contraction of DNA repeats, usually trinucleotide repeats, as a consequence of aberrant replication. Despite the importance of this area, the coverage of these issues is uneven and this section provides another example of the manner in which discussion of topics is fragmented in this volume. It is in this section that much of the molecular, genetic and biochemical analyses of proteins that are described in the first two sections are discussed. One example of uneven coverage is the chapter on DNA helicases, which virtually ignores a substantial body of work done on these proteins in yeasts.

The final section of the book provides current overviews of the replication of medically important DNA viruses. As for cellular DNA replication, significant advances in our understanding of how these viruses replicate have been made in the last ten years. A new and useful feature of these chapters is a discussion of how these viruses cause human disease.

A significant strength of this volume is the appendices. The first appendix draws on the explosion of genomic information and summarizes molecular interactions of DNA replication proteins and the evolutionary history of proteins involved in pre-replication complex assembly. The second appendix contains seven very useful tables that summarize a wealth of information, including the size and complexity of eukaryotic genomes, genetic and protein nomenclature for different organisms, alternative names for orthologues, cellular concentrations of replication origins and pre-replication complex proteins, human diseases associated with defects in DNA replication and repair, and a list of therapeutic drugs that target DNA replication.

Despite some drawbacks, this book provides a broad and current synthesis of our understanding of genome duplication and it should be on the bookshelves of all students of DNA replication.

Carol Newlon is in the Department of Microbiology & Molecular Genetics, UMDNJ-New Jersey Medical School, Newark, NJ 07103, USA.
e-mail: newlon@umdnj.edu

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