DNA REPLICATION
IN EUKARYOTIC
CELLS
DNA REPLICATION IN EUKARYOTIC CELLS

Edited by

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Preface, ix
Acknowledgments, xiii

CONCEPTS

1 Mechanisms for Replicating DNA, 1
   G.S. Brush and T.J. Kelly

2 Origins of DNA Replication, 45
   M.L. DePamphilis

3 Roles of Transcription Factors in DNA Replication, 87
   P.C. van der Vliet

4 Roles of Nuclear Structure in DNA Replication, 119
   R. Laskey and M. Madine

5 Mechanisms for Priming DNA Synthesis, 131
   M. Salas, J.T. Miller, J. Leis, and M.L. DePamphilis

6 Mechanisms for Completing DNA Replication, 177
   D. Bastia and B.K. Mohanty

7 Fidelity of DNA Replication, 217
   J.D. Roberts and T.A. Kunkel

8 DNA Excision Repair Pathways, 249
   E.C. Friedberg and R.D. Wood

9 Chromatin Structure and DNA Replication: Implications for
   Transcriptional Activity, 271
   A.P. Wolffe
CONTENTS

10 Roles of Phosphorylation in DNA Replication, 295  
K. Weisshart and E. Fanning

11 Control of S Phase, 331  
K. Nasmyth

12 Temporal Order of DNA Replication, 387  
I. Simon and H. Cedar

13 Changes in DNA Replication during Animal Development, 409  
J.L. Carminati and T.L. Orr-Weaver

14 Comparison of DNA Replication in Cells from Prokarya and Eukarya, 435  
B. Stillman

PROTEINS

15 Cellular DNA Polymerases, 461  
T.S.-F. Wang

16 Viral DNA Polymerases, 495  
D.M. Coen

17 DNA Replication Accessory Proteins, 525  
U. Hübscher, G. Maga, and V.N. Podust

18 DNA Helicases, 545  
J.A. Borowiec

19 DNA Ligases, 575  
R. Nash and T. Lindahl

20 DNA Topoisomerases, 587  
A. Hangaard Andersen, C. Bendixen, and O. Westergaard

21 DNA Telomerases, 619  
C.W. Greider, K. Collins, and C. Autexier

SYSTEMS

22 SV40 and Polyomavirus DNA Replication, 639  
J.A. Hassell and B.T. Brinton

23 Papillomavirus DNA Replication, 679  
A. Stenlund

24 Adenovirus DNA Replication, 699  
R.T. Hay
<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>Herpesvirus DNA Replication, 721</td>
<td>M. Challberg</td>
</tr>
<tr>
<td>26</td>
<td>Epstein-Barr Virus DNA Replication, 751</td>
<td>J.L. Yates</td>
</tr>
<tr>
<td>27</td>
<td>Poxvirus DNA Replication, 775</td>
<td>P. Traktman</td>
</tr>
<tr>
<td>28</td>
<td>Parvovirus DNA Replication, 799</td>
<td>S.F. Cotmore and P. Tattersall</td>
</tr>
<tr>
<td>29</td>
<td>Replication of the Hepatitis Virus Genome, 815</td>
<td>C. Seeger and W.S. Mason</td>
</tr>
<tr>
<td>30</td>
<td>Geminivirus DNA Replication, 833</td>
<td>D.M. Bisaro</td>
</tr>
<tr>
<td>31</td>
<td>Baculovirus DNA Replication, 855</td>
<td>C.H. Ahrens, D.J. Leisy, and G.F. Rohrmann</td>
</tr>
<tr>
<td>32</td>
<td>DNA Replication in Yeast, 873</td>
<td>C.S. Newlon</td>
</tr>
<tr>
<td>33</td>
<td>DNA Replication in Tetrahymena, 915</td>
<td>G.M. Kapler, D.L. Dobbs, and E.H. Blackburn</td>
</tr>
<tr>
<td>34</td>
<td>DNA Replication in Physarum, 933</td>
<td>G. Pierron and M. Bénard</td>
</tr>
<tr>
<td>35</td>
<td>Differential DNA Replication in Insects, 947</td>
<td>S.A. Gerbi and F.D. Urnov</td>
</tr>
<tr>
<td>36</td>
<td>DNA Replication in Xenopus, 971</td>
<td>J.J. Blow and J.P.J. Chong</td>
</tr>
<tr>
<td>37</td>
<td>DNA Replication in Mammals, 983</td>
<td>N.H. Heintz</td>
</tr>
<tr>
<td>38</td>
<td>DNA Replication in Plants, 1005</td>
<td>J. Van’t Hof</td>
</tr>
<tr>
<td>39</td>
<td>Mitochondrial DNA Replication, 1015</td>
<td>D.A. Clayton</td>
</tr>
<tr>
<td>40</td>
<td>Kinetoplast DNA Replication, 1029</td>
<td>A.F. Torri, L.J. Rocco Carpenter, and P.T. Englund</td>
</tr>
</tbody>
</table>

Index, 1043
Preface

Science should be made as simple as possible, but not simpler.
Albert Einstein (1879–1955)

In 1959, Arthur Kornberg received the Nobel Prize in medicine and physiology for his pioneering work on the biological synthesis of DNA, an event that marked the beginning of a tremendous effort to understand how cells and viruses replicate their genetic information. This effort produced a new field of scientific research known as DNA replication, accompanied by an extensive literature that has accumulated over the past 35 years. In 1991, Arthur Kornberg and Tania Baker dealt with this vast and complex literature by publishing a wonderful synopsis of DNA replication that covers all aspects of the subject, but whose particular strength lies in its clearly articulated description of the many manifestations of DNA synthesis observed in prokaryotic cells, their bacteriophages, and their plasmids. The goal of this book is to provide a more detailed treatment of the subject of DNA replication in eukaryotic cells.

During the past two decades, advances in technology have permitted analyses of viral, mitochondrial, and cellular genomes that previously had not been possible. Interest in this field accelerated as it became clear that regulation of DNA replication was central to understanding regulation of cell and viral proliferation, events that have a direct impact on our understanding of human diseases. Given the complexity of eukaryotic cells and their need to coordinate proliferation with differentiation during animal development, it is not surprising that the subject of DNA replication in eukaryotic cells is more complex than may have been anticipated. On the order of 30 to 40 proteins are involved directly in the process of DNA replication, as are components of the transcription machinery, chromosome structure, and nuclear structure. DNA replication in eukary-
otes involves nuclear and mitochondrial genomes as well as viral genomes containing single-stranded or double-stranded DNA or RNA. It involves specific DNA sequences that determine where replication begins (replication origins) and that mark the ends of linear chromosomes (telomeres). It involves decisions of when, where, and how to initiate DNA replication, repair DNA damage that would otherwise interfere with replication, and ensure that one, and only one, complete and accurate copy of its genome is made before a cell attempts to divide. It utilizes many of the same principles found in prokaryotic cells but offers the possibility that new principles, uniquely suited to problems encountered in eukaryotes, still await discovery. Nevertheless, progress in this field has been impressive.

Our knowledge of events at DNA replication forks in eukaryotic DNA now rivals that in prokaryotic systems: All of the DNA and RNA replication intermediates have been identified, and the proteins that synthesize and repair DNA, as well as the genes that produce these proteins, are well on the way to full disclosure. Even the more subtle processes that initiate and regulate replication are yielding to investigation. Several viral origins have been characterized and shown to contain transcription elements and to function in soluble systems with purified components, behaving in many ways like prokaryotic replication origins. The genomes of mitochondria and single-cell organisms also contain well-characterized replication origins, and many of the proteins that interact with them have been identified. However, initiation of replication at these origins has not yet been made to occur outside of the cell. Intriguingly, the genomes of metazoan organisms contain more complex replication origins whose function depends on nuclear structure as well as soluble proteins. Many of the proteins that regulate DNA replication have been identified, and their chemical modifications and associations with other proteins have been monitored throughout the cell division cycle. Thus, Bruce Stillman, Director of the Cold Spring Harbor Laboratory, and John Inglis, Executive Director of the Cold Spring Harbor Laboratory Press, believed that the time had come to collate this information and summarize our current understanding of DNA replication in eukaryotic cells. I was invited to orchestrate the effort.

The purpose of the book is threefold. First, it is for teachers who would appreciate a current survey of the concepts involved, but who do not have the time to sort through the vast amount of information on which these concepts are based. Second, it is for scientists already working in this and other fields who would appreciate a synopsis of the facts and concepts that have emerged so far. Finally, it is for those who would
like to relate DNA replication to other biological problems in eukaryotes, but who may feel intimidated by the sheer size and complexity of the subject. Accordingly, we have organized the book into three parts: concepts, proteins, and systems.

The first part presents the major concepts involved in DNA replication as well as correlative subjects such as DNA repair, chromatin structure, protein phosphorylation, and cell cycle control. Each chapter collates results from many different experimental systems, distills the essential ideas from these results, searches for common underlying themes, and presents to the reader as coherent a view of the subject as possible. The second part describes each class of proteins that are directly involved in DNA replication. These chapters summarize the current information concerning the structure of these proteins, their catalytic activities, their mechanism of action, and useful inhibitors and genetic mutations. The third group of chapters describes what is known about how a particular genome replicates. Each chapter identifies the DNA replication intermediates, the specific DNA or RNA sequences that are required, and the replication proteins that are involved. Although this approach results in a certain amount of redundancy, it also allows the same material to be presented by different authors with different points of view.

To ensure that each aspect of the subject was accurately, completely, and clearly presented, 92 scientists in the field of DNA replication participated in assembling this book. Each of the 40 chapters was written independently by its respective author(s), then reviewed by the editor as well as one or more experts in that aspect of the subject. These included authors of other chapters as well as the reviewers acknowledged below. In addition, this work would not have been possible without the patient, cheerful, and professional editorial staff at the Cold Spring Harbor Laboratory Press. In particular, we are indebted to Patricia Barker and Joan Ebert for bringing this book to fruition. I also thank Dr. Ernst Winnacker, Director of the Gene Center at the University of Munich in Germany, and the Humboldt Society for enabling me to take a brief sabbatical in an excellent scientific environment that contributed to the success of this project.

On behalf of the authors, the external reviewers, and the members of the Cold Spring Harbor Laboratory Press, I express the hope that those who read this book will enjoy it as much as did those who wrote it.

March, 1996

Melvin L. DePamphilis
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