DNA Replication

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A subject collection from Cold Spring Harbor Perspectives in Biology

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Preface

The fundamental principles that govern DNA replication are elegant and simple. Take a DNA double helix, unzip it, and, following the chemical rules of base complementarity, use the single strands as templates to generate new daughter molecules. Yet to accomplish this task in appropriate time and space, and with sufficient fidelity, requires the coordinated interplay and regulation of a multitude of complex protein assemblies. In the ensuing pages, 77 authors describe the exquisite complexity of the macromolecular machines that drive this conceptually simple process. This is a truly exciting field in which to work—the rate of progress of the development of techniques and concepts is remarkable. This is reflected by the fact that this book comes just 6 years after the last Cold Spring Harbor Laboratory Press volume on the subject. During that time we have learned much about the core mechanisms of replication-associated processes and have gained a much fuller appreciation of the interplay between the regulatory circuits that drive cell cycle progression and the replication apparatus itself. As will be apparent from the contents of the book, the full complement of state-of-the-art techniques, from structural biology through biophysical analyses, single-molecule studies, biochemistry, genetics, genomics, imaging, and cell biology, have been exploited with remarkable effect to tease apart these intricate processes.

DNA replication is, of course, fundamental to the propagation of all life on the planet. It is a process that when it goes awry can have profound consequences for the organism. In the case of humans, as detailed by Abbas et al. and A.P. Jackson et al., errors in replication can lead to cancer, yet, conversely, the very presence of elevated levels of replication-associated proteins can be a powerful indicator of cancerous or precancerous conditions. Human pathogens, whether bacterial or viral, need to replicate their genomes within their host. Authors Cotmore and Tattersall, Chow and Broker, Hoeben and Uil, Weller and Coen, Hammerschmidt and Sugden, and Moss all deal with the mechanisms of viral DNA replication. In many cases virus-specific proteins facilitate initiation of replication but then co-opt components of the cellular machinery for elongation. By characterizing the virus-specific components, potential candidates for drug development can be identified. At least part of the reason viruses encode their own initiator proteins is to circumvent the cellular circuitry that controls DNA replication and, in most cases, limits it to occurring once per cell division cycle. The chapter by Zielke et al. deals with some important exceptions to this once per cell division cycle rule. The interface between control circuitry and core machinery is complex and tightly interwoven in eukaryotes, and Leonard and Mechali, McIntosh and Blow, Bell and Kaguni, Tanaka and Araki, D. Jackson et al., Rhind and Gilbert, Siddiqui et al., and de la Paz Sanchez et al. all deal with the various aspects of this interplay. Indeed, although a number of aspects linked to the mechanisms of DNA synthesis appear to be conserved in all living organisms, new regulatory events have been introduced in the process of the initiation of DNA replication in metazoans. Origins of DNA replication appear to be more complex structures, involving different sequence constraints and epigenetic controls, and these are probably tightly linked to cell cycle controls and adaptations to cell identity. New factors involved in the assembly and control of replication origin complexes thus appeared during evolution. These aspects are treated in chapters by Leonard and Mechali, Tanaka and Araki, Siddiqui et al., and de la Paz Sanchez et al.

Given the essential and mechanistically conserved nature of DNA replication, it is perhaps surprising that bacteria utilize a set of proteins that are not orthologous to their counterparts in archaea and eukaryotes. As detailed in chapters by O’Donnell et al., Duderstadt et al., and Skarstad and
Katayama, although the basic tenets of replication are similar between the three domains of life, the machineries have some important differences. Makarova and Koonin explore the evolution of these distinct apparatuses and the relationship between archaeal and eukaryal replication-associated proteins. However, it must not be forgotten that eukaryotic cells harbor remnant bacteria in the form of mitochondria with their own replication proteins and processes, and these are described in the chapter by Holt and Reyes.

Despite the variation in the precise nature of the proteins that mediate DNA replication, all cellular organisms replicate their DNA via a common structure—the replication fork. The structure is propagated by the action of the replicative helicase, built around the minichromosome maintenance (MCM) complex in archaea and eukaryotes. The nature and activation of this assembly is discussed in chapters by Tanaka and Araki and Bell and Botchan. The helicase provides single-stranded DNA that acts as a template for synthesis of new DNA by the replicative DNA polymerases on the exposed single-stranded templates on both leading and lagging strand (chapters by Johansson and Dixon and Peters and Nishiyama). Because of the low inherent processivity of the polymerases, they require an interaction with a sliding clamp that, in turn, must be actively loaded onto DNA, a conserved process that is discussed by Hedglin et al. Because of the discontinuous nature of lagging-strand replication, this is a highly dynamic assembly. As detailed in the chapter by Duderstadt et al., recent single-molecule studies both in vivo and in vitro have yielded significant insight into the coordination of events during replication-fork progression in a variety of model systems. Balakrishnan and Bambara discuss the interplay of a variety of pathways that lead to maturation of the lagging-strand DNA from RNA-primed Okazaki fragments to covalently intact DNA molecules.

During the life of a replication fork, DNA lesions or other impediments to its progress may be encountered, potentially resulting in fork stalling or even collapse. Cells have evolved complex checkpoint pathways to deal with such events and a variety of mechanisms can be brought into play to rescue stalled or damaged replication forks (Yeeles et al.). These can include the co-option of specialized lesion bypass polymerases that have the capacity to synthesize over even quite bulky lesions in DNA; however, this has the potential to introduce mutation into DNA and so must be tightly controlled (Goodman and Woodgate). Another DNA repair pathway that utilizes the replication apparatus is break-induced replication (Anand et al.).

The extraordinary degree of compaction of eukaryotic genomes into chromatin, combined with the importance of epigenetic regulation of gene expression, has led to a tight association of chromatin assembly proteins with the replication fork. The coordination between these pathways is described in MacAlpine and Almouzni. Another eukaryotic-specific issue lies in the replication of telomeres. Since the last volume, tremendous progress has been made in understanding the protein complexes that carry out this specialized task (Pfeiffer and Lingner). Another process that in eukaryotes is inextricably intertwined with replication is the establishment of sister chromatid cohesion (Peters and Nishiyama).

It has been a true pleasure for the editors to work with leading members of the field to put this book together and we would like to express our gratitude to the authors for their contributions. We are also profoundly grateful to Barbara Acosta, Inez Sialiano, and Diane Schubach at Cold Spring Harbor Laboratory Press for their skillful and dedicated assistance.

Stephen D. Bell
Marcel Mîchali
Melvin L. DePamphilis
Dedication to Arthur Kornberg

This book is dedicated to Arthur Kornberg, who was more than a pioneer in the field of DNA replication—he was a legend in his own lifetime. Arthur was a great source of inspiration to scientists interested in DNA replication for an unusually long period of time. In his laboratory, outstanding discoveries were made that paved the way in this field for decades that followed. Among them, three milestones must be remembered. First and foremost was the discovery that DNA synthesis is an enzymatic process carried out by a protein that Arthur purified with the assistance of two postdoctoral fellows, Maurice Bessman and Robert Lehman, and named DNA polymerase (1956–1958) (Kornberg et al. 1956; Lehman et al. 1958). In 1959, one year after publication of this discovery, Arthur Kornberg was awarded the Nobel Prize in Physiology or Medicine. The second milestone was the complete synthesis of a biologically active viral DNA (Goulian and Kornberg 1967) that was carried out in collaboration with Mehran Goulian and Robert Sinsheimer, and hailed in the popular press as “creation of life in a test tube.” The third milestone was the in vitro reproduction of the initiation of DNA synthesis from the Escherichia coli origin of DNA replication (Fuller et al. 1981). During this period, scientists in Arthur’s laboratory identified most of the proteins involved in bacterial DNA synthesis, a feat that alone would also have deserved a Nobel Prize. The work generated by his laboratory was prodigious. Everyone in this field can probably remember following the DNA replication enzymology series published nearly every month in The Journal of Biological Chemistry (173 papers in all), sometimes with up to 10 episodes in a single issue! This avalanche of pioneering results often left people with the impression that every important mechanism had been solved in DNA replication. However, as this book reveals, DNA replication in archaea and multicellular eukaryotes is more than just an “interesting variation” of what has been observed in bacteria (Kornberg 1979).

Research performed in the Kornberg laboratory was also a magnificent example of the power of biochemistry and enzymology, and Arthur was always very keen to promote this field. Arthur Kornberg is also well known for his quotations, in particular his famous version of “The Ten Commandments” (Kornberg 2003), of which number III, “Thou shalt not believe something just because you can explain it,” and number IV, “Thou shalt not waste clean thinking on dirty enzymes,” are often quoted. Arguably Arthur’s greatest contribution to science was the host of students and postdoctoral fellows he mentored, many of whom became outstanding scientists in their own right. He infected all of us with his love of science. In an editorial Arthur wrote in 1995 (Kornberg 1995), he said, “[R]ich or poor, science is great! To frame a question and arrive at an answer that opens a window to yet another question, and to do this in the company of like-minded people with whom one can share the thrill of unanticipated and extended vistas, is what science is all about. That is what will sustain us in the days and years ahead.”

Marcel Mechali
Stephen D. Bell
Melvin L. DePamphilis
References


We fondly remember Arturo Falaschi as a colleague of extraordinary energy, creativity, and dedication to the field of DNA replication and to the development of European science. Bolstered by the 3 years (1962–1965) he spent as a postdoctoral fellow with Arthur Kornberg, Arturo turned his attention to the complexities of DNA replication in eukaryotic cells. His laboratory developed pioneering methods to map DNA replication origins along chromosomes and characterized in detail the lamin B2 origin of DNA replication. He was also deeply involved in the biochemistry of DNA replication, with the characterization of several proteins, including DNA helicases, and topoisomerases. Arturo Falaschi was also responsible for the International Centre for Genetic Engineering and Biotechnology (ICGEB), an international research organization conceived within the United Nations, creating two laboratories in Trieste and New Dehli, promoting research and training young scientists from developing countries.
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