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 interwoven 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.

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