Preface

DNA replication, the process of copying one double-stranded DNA molecule to form two identical copies, is highly conserved at the mechanistic level across evolution. In eukaryotes, the process includes also copying of epigenetic information in terms of chemical modifications to DNA and chromatin structure, and preparation of the sister chromatids ready for separation at mitosis. It comprises a highly complex set of biochemical reactions carried out by intricate enzyme assemblies and coordinated within the cell division cycle and in response to external and internal cellular signals. This book attempts to cover DNA replication from a biochemical perspective, relating the structures of key proteins involved in replication to their function: it does not attempt to deal with all the complexities of the biology of replication which have been so excellently discussed elsewhere.[†] The focus is very much on eukaryotic replication though archaeal paradigms and, where relevant, lessons from prokaryotes are also discussed. The book is not intended to cover every aspect and detail of replication, but rather aims to examine conserved structural and mechanistic themes in DNA replication, providing a suitable background for biochemical, chemical and pharmaceutical studies of this huge and exciting field.

Insights into the process at the molecular level provide opportunities to modulate and intervene in replication: rapidly diving cells need to replicate their DNA prior to dividing, and targeting components of the replication process is potentially a very powerful strategy in the treatment of cancer. Ageing may conversely be associated with loss of replication activity: restoring replication capacity to cells (particularly attending to the 'end replication problem' at telomeres) may be a route for moderating some of the diseases and frailty associate with ageing.

[†] M. L. DePamphilis (ed.), *DNA Replication and Human Disease*, Cold Spring Harbor Laboratory Press, New York, 2006.

Molecular Themes in DNA Replication
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The importance of copying DNA in subcellular organelles is often overlooked. In this book, replication of the mitochondrial genome is examined and the clinical consequences of errors explored. Targeting DNA replication of pathogenic bacteria and viruses is already a clinical reality; the possibility of exploiting novel domains and motifs in replication factors of the malaria parasite is highlighted here as an important route for possible future therapies against malaria. DNA replication is therefore fundamental to a huge range of molecular biological and biochemical applications, and provides many potential targets for rational drug design in the treatment of hyper- and hypo-plastic diseases, and those caused by pathogens. Such targets, and current and future therapeutic approaches, are covered wherever relevant.

Interesting in its own right as a major feat of biochemical regulation and coordination, DNA replication is at the heart of modern advances in molecular biology. Without understanding the chemistry of DNA replication, Sanger would not have been able to develop his ground-breaking technique of chain termination dideoxy sequencing of DNA that has led to the explosion of molecular biology and revolutionized our understanding of, and ability to manipulate, the genome. As well as DNA sequencing (both dideoxy and next generation pyrosequencing), cloning of genes requires their replication; the polymerase chain reaction (PCR) used in almost every sphere of modern biochemistry is simply region-specific DNA replication on a grand scale. An understanding of DNA replication at both the biological and chemical level is essential to developing such technologies and using them effectively.

By providing an overview of the core mechanistic aspects of DNA replication and relating structure to function, this book is intended to serve as an introduction to higher level undergraduates and graduate students, as a source of information for those approaching DNA replication from other disciplines, and as a useful resource for researchers already in the field.