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DNA Helicases and DNA Motor Proteins

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Preface

A plethora of molecular motors hustle and bustle along the chromosomes of all living cells. Distinct among them are helicases, classified by the presence of the so-called helicase signature motifs in their amino acid sequences. Helicases were discovered in the 1970s and were reputed to be the enzymes that "unwind" duplex nucleic acids in an energy-dependent manner. The transient separation of DNA duplexes allows cellular machines of DNA replication, recombination, repair, and transcription to access the encoded information and is thereby an essential process required for all aspects of cellular DNA metabolism. An explosion of the helicase-related research was prompted by the paramount importance to understand at the molecular level the fundamental cellular processes that depend on helicase activities. Recent methodological advances allowed for critical breakthroughs in understanding the helicase structure and function. Numerous proteins containing the helicase signature motifs have been identified and extensively studied. Many of these proteins do, indeed, display *bona fide* strand separation activity. An important realization, however, came when the helicase family was expanded by the discovery of proteins that, despite the presence of the conserved signature motifs, lack duplex unwinding activity. It became clear that the helicase signature motifs define a generic motor core, which enables ATP- (or NTP-)driven conformational changes that allow the enzyme to translocate along nucleic acids. The mechanistic underpinnings of this process have been pondered, debated, and only recently agreed upon. Whether the same mechanism underlies "useful" activities of the helicases, however, is still an unresolved question. Unidirectional translocation of a helicase or a helicase-like translocase may be coupled to other thermodynamically unfavorable processes including separation of DNA duplexes, packaging of viral genomes, DNA segregation after replication, and disassembly and rearrangement of protein–nucleic acid complexes. The distinct mechanistic properties can be endowed to a structurally and mechanistically conserved motor core in part through unique auxiliary domains or interacting partners that provide additional functions allowing the helicase/translocase to perform a diverse set of activities. Moreover, interactions with different substrates, protein partners, and/or posttranslational modification readily convert a helicase into a translocase and a translocase into a helicase.

Each cell contains numerous DNA helicases, RNA helicases, helicase-like translocases, and molecular switches. Some of them function independently, some are integrated into larger macromolecular assemblies orchestrating complex nucleoprotein remodeling events, while others can participate in different cellular pathways guided by posttranslational modifications or by the presence of distinct interacting partners.

The field of DNA helicase research has reached a stage when the studies of molecular mechanisms and basic biology of helicases can and shall be integrated with the studies of development, cancer, and longevity. The objective of this book is to provide the first systematic overview of structure, function, and regulation of DNA helicases and related molecular motors. The chapters in this book are written by leading experts in the growing field of DNA helicase research. By integrating the knowledge obtained through diverse technical approaches ranging from single-molecule biophysics to cellular and molecular biological studies the 13 chapters comprising this volume aim at providing a unified view on how helicases function in the cell, are regulated in response to different cellular stresses, and are integrated into large macromolecular assemblies to form a complex and adaptive living system.

Wu and Spies start this volume by introducing in Chap. 1 the diverse substrates that DNA helicases act upon: duplex and single-stranded DNA, chromatin, and various nucleoprotein complexes. This chapter will also provide a historic outlook on discovery of DNA helicases, classification into superfamilies, and on the evolution of our understanding of what helicases are and what functions they perform. Chapters 2, 3, and 4 comprehensively review the state of the art in our knowledge of the structure, function, and mechanisms of translocation and duplex unwinding by major helicase superfamilies. In Chap. 3 Aarattuthodiyil, Byrd, and Raney introduce Superfamily 1 helicases; in Chap. 4 Beyer, Ghoneim and Spies Describe Superfamily 2; and in Chap. 4 Medagli and Onesti discuss hexameric DNA helicases. These chapters provide a mechanistic platform for understanding the assembly, function, and regulation of the molecular machines, which incorporate the helicase-like motor components. In Chap. 5, McGlynn describes how individual helicases introduced in the previous chapters cooperate at the replication fork to maintain an uninterrupted progression of the delicate machinery of the replisome.

One of the major consequences of cellular dependence on DNA helicases is that the absence of, or defects in, these enzymes often lead to cellular dysfunction and cause a broad spectrum of human disorders, usually characterized by premature aging, susceptibility to cancers, and other diseases normally associated with aging, immunodeficiency, or mental retardation. Expression of some DNA helicases is upregulated in proliferating cells, providing a diagnostic marker for malignant cells and presenting an attractive target for development of anticancer therapeutics. In Chap. 6 Suhasini and Brosh discuss these biomedically important helicases and their potential as targets for novel anticancer therapeutics and adjuvants of the standard treatments. Viral helicases serve as another potential drug target highlighted by the recent development of several specific inhibitors targeting the association of the helicase/primase encoded by herpes simplex virus. In Chap. 7,

Field and Mickleburgh provide an account of, so far, the only successful drug discovery campaign targeting a DNA helicase.

The next three chapters focus on the DNA helicases functioning in the cellular processes vital for maintaining the integrity of the genome. In Chap. 8, Larsen and Hickson discuss RecQ helicases, which are probably the most extensively studied family of caretaker helicases to date. In Chap. 9, Daley, Niu and Sung discuss DNA helicases and translocases that control, both positively and negatively, the processes of homologous recombination and homology-directed DNA repair. DNA helicases participating in the nucleotide excision, base excision, and mismatch repair are covered in Chap. 10 by Kuper and Kisker.

The subjects of the three final chapters are helicase-like proteins that do not require a bona fide strand separation activity to perform their cellular roles. In Chap. 11, Szczelkun highlights the similarities between some helicase-like proteins and other hydrolysis-driven molecular switches. The theme of dsDNA translocases is further elaborated in Chap. 12, where Demarre, Galli and Barre discuss FtsK, a complex motor involved in bacterial division. In the last chapter, Yodh talks about dsDNA translocating motors incorporated into the chromatin assembly and remodeling complexes.

In recent years, a number of groundbreaking structural and mechanistic studies deepened our understanding of helicase mechanisms and established new approaches for their analyses. Many fundamental mechanistic questions, however, remain to be answered. These questions range from the mechanism of force generation and mechanochemical coupling to distinct mechanisms by which the same enzyme translocates on DNA removing obstacles, unwinds DNA, and/or remodels nucleoprotein complexes. It is even less understood how the helicase motors are regulated and incorporated into a wide range of genome maintenance and repair machines.

It is our hope that this book will become a key reference to the researchers with expertise in diverse fields who study DNA helicases, inspiring collaborative and multidisciplinary approaches to many unresolved questions in the helicase field. This book will also be a useful starting point for graduate, medical, and advanced undergraduate students who look to extend their knowledge of these exciting enzymes beyond standard and often outdated textbook information. Finally, we hope that this book will provide a valuable resource for medicinal chemists seeking new targets for development of novel anticancer and antiviral therapeutics.

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