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Review

Biophysical characterization of DNA binding from single molecule force measurements

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Abstract

Single molecule force spectroscopy is a powerful method that uses the mechanical properties of DNA to explore DNA interactions. Here we describe how DNA stretching experiments quantitatively characterize the DNA binding of small molecules and proteins. Small molecules exhibit diverse DNA binding modes, including binding into the major and minor grooves and intercalation between base pairs of double-stranded DNA (dsDNA). Histones bind and package dsDNA, while other nuclear proteins such as high mobility group proteins bind to the backbone and bend dsDNA. Single-stranded DNA (ssDNA) binding proteins slide along dsDNA to locate and stabilize ssDNA during replication. Other proteins exhibit binding to both dsDNA and ssDNA. Nucleic acid chaperone proteins can switch rapidly between dsDNA and ssDNA binding modes, while DNA polymerases bind both forms of DNA with high affinity at distinct binding sites at the replication fork. Single molecule force measurements quantitatively characterize these DNA binding mechanisms, elucidating small molecule interactions and protein function.

Keywords: Force spectroscopy; DNA binding; DNA melting; DNA replication; Nucleic acid chaperones

Contents

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1. Introduction

Single molecule methods have provided a clearer understanding of a wide range of fundamental biological processes, including DNA replication, transcription, and repair. Single molecule force spectroscopy began with the capture and manipulation of single DNA molecules. Techniques such as optical tweezers, magnetic tweezers, and atomic force microscopy (AFM) apply forces to single molecules, probing conformational changes and structural dynamics in a variety of conditions. Such measurements explore the interactions of DNA with molecules ranging from small ligands to complex proteins. Quantifying the thermodynamics and kinetics of these interactions leads to substantial insights into DNA binding mechanisms in important biological systems.