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Review

Condensed DNA: Condensing the concepts

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ABSTRACT

DNA is stored *in vivo* in a highly compact, so-called condensed phase, where gene regulatory processes are governed by the intricate interplay between different states of DNA compaction. These systems often have surprising properties, which one would not predict from classical concepts of dilute solutions. The mechanistic details of DNA packing are essential for its functioning, as revealed by the recent developments coming from biochemistry, electrostatics, statistical mechanics, and molecular and cell biology. Different aspects of condensed DNA behavior are linked to each other, but the links are often hidden in the bulk of experimental and theoretical details. Here we try to condense some of these concepts and provide interconnections between the different fields. After a brief description of main experimental features of DNA condensation inside viruses, bacteria, eukaryotes and the test tube, main theoretical approaches for the description of these systems are presented. We end up with an extended discussion of the role of DNA condensation in the context of gene regulation and mention potential applications of DNA condensation in gene therapy and biotechnology.

Contents

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1. Introduction

Storage and processing of genetic information encoded in DNA is governed by a number of compounds, which bind, bend, loop, modify DNA and assemble on the double helix, recognize each other and target new DNA binders (Fig. 1). These events are further complicated by the fact that they happen *in vivo* in a highly compact, so-called condensed DNA state. Scientists have been dealing with condensed DNA since the discovery of nucleic acids. However, only recently with the development of adequate tools for the single-molecule and whole-genome analysis, it has became possible to connect classical bulk experiments to mechanistic details of gene regulation *in vivo*. This has led to a number of new concepts and the reevaluation of some of the old ones. The purpose of this review is to provide what we believe are the most exciting concepts, which obviously does not reflect the whole body of the literature. For more extensive data-oriented literature overview see the recent books with the focus on DNA condensation *in vitro* (Dias and Lindman, 2008) or *in vivo* (Rippe, in press) and older reviews devoted to DNA condensation (Bloomfield, 1996, 1997; Gelbart et al., 2000; Hud and Vilfan, 2005; Schiessel, 2003; Strey et al., 1998; Vijayanathan et al., 2002; Yoshikawa, 2001; Yoshikawa and Yoshikawa, 2002). We will start with biological concepts arising from DNA packing in viruses, bacteria and eukaryotes, then proceed to DNA condensation *in vitro* and its theoretical modeling, and finally discuss the role of DNA condensation in the context of gene regulation in living systems and its potential biomedical applications.

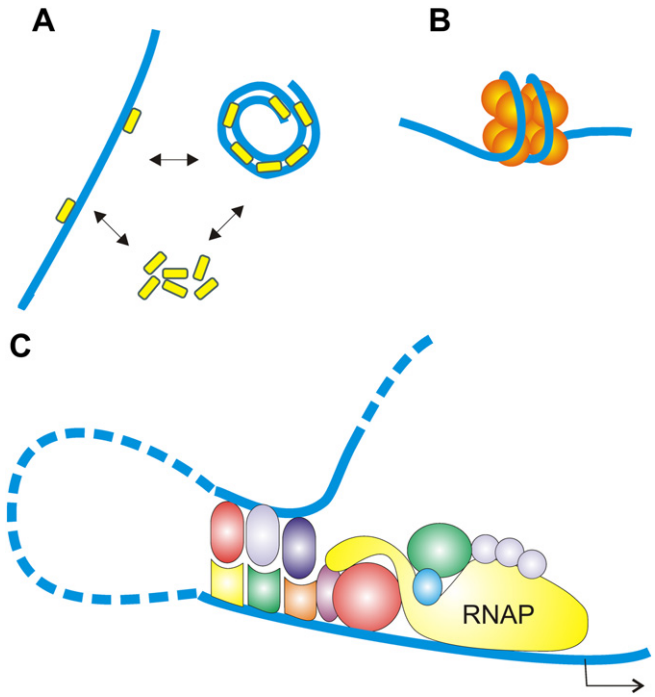

Fig. 1. Biological implications for DNA compaction. A) Small ligands (inorganic ions, polyamines, etc) may induce DNA condensation *in vitro*. This process is used to model DNA compaction in prokaryotes within the small volume of the bacterial nucleoid or viral capsid. B) In eukaryotes, DNA is wrapped around histone proteins to form the nucleosome. Further levels of compaction of the chromatin fiber are achieved with the help of divalent metal ions and proteins. C) Gene regulation in many cases involves DNA looping maintained by protein bridging at the promoter and enhancer regions. Precise spatial positioning of the DNA and DNA–DNA recognition might facilitate the multiprotein assembly and recruitment.

2. The concept of DNA condensation

DNA is a long and strongly charged heteropolymer. It bears on average one elementary negative charge per each 0.17 nm of the double helix. DNA diameter is about 2 nm, while the length of a stretched single-molecule may be up to several dozens of centimeters depending on the organism (Bloomfield et al., 2000). Many features of the DNA double helix contribute to its large stiffness, including the mechanical properties of the sugar–phosphate backbone, electrostatic repulsion between phosphates, stacking interactions between the bases of each individual strand, and strand–strand interactions (Guo et al., 2008). The measure of the DNA stiffness is the persistence length, which characterizes the length over which a tangent vector to the DNA axis becomes uncorrelated. The persistence length of the double-stranded DNA in physiological conditions is around 50 nm depending on the DNA sequence (Bloomfield et al., 2000; Brinkers et al., 2009; Zheng et al., 2010). Such a large persistence length makes DNA one of the stiffest natural polymers, yet this value is quite small in comparison with the typical DNA lengths. This means that at the distance much larger than the persistence length the DNA can be considered as a flexible rope, and on a short scale as a stiff rod. Like a garden hose, unpacked DNA would randomly occupy a much larger volume than when it is orderly packed. Mathematically, for a non-interacting flexible chain randomly diffusing in 3D, the end-to-end distance would scale as a square root of the polymer length. For real polymers such as DNA this gives only very rough estimate; what is important, is that the space available for the DNA *in vivo* is much smaller than the space that it would occupy in the case of a free diffusion in the solution. In order to cope with the volume constraints, DNA has a striking property to pack itself in the appropriate solution conditions with the help of ions and other molecules. Usually, DNA condensation is defined as “the collapse of extended DNA chains into compact, orderly particles containing only one or a few molecules” (Bloomfield, 1997). As detailed below, this definition applies to many situations *in vitro* and is also close to the definition of DNA condensation in bacteria as “adoption of relatively concentrated, compact state occupying a fraction of the volume available” (Zimmerman and Murphy, 1996). In eukaryotes, the DNA size and the number of other participating players are much larger, and a DNA molecule forms millions of ordered