Advances in Colloid and Interface Science xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Advances in Colloid and Interface Science

journal homepage: www.elsevier.com/locate/cis

DNA conformational behavior and compaction in biomimetic systems: Toward better understanding of DNA packaging in cell

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ARTICLE INFO

Available online xxxx

Keywords:
DNA condensation and compaction
Crowding
Confinement
Artificial cell
Single-molecule

ABSTRACT

In a living cell, long genomic DNA is strongly compacted and exists in the environment characterized by a dense macromolecular crowding, high concentrations of mono- and divalent cations, and confinement of ca. 10 μm size surrounded by a phospholipid membrane. Experimental modelling of such complex biological system is challenging but important to understand spatiotemporal dynamics and functions of the DNA in cell. The accumulated knowledge about DNA condensation/compaction in conditions resembling those in the real cell can be eventually used to design and construct partly functional "artificial cells" having potential applications in drug delivery systems, gene therapy, and production of synthetic cells. In this review, I would like to overview the past progress in our understanding of the DNA conformational behavior and, in particular, DNA condensation/compaction phenomenon and its relation to the DNA biological activity. This understanding was gained by designing relevant experimental models mimicking DNA behavior in the environment of living cell. Starting with a brief summary of classic experimental systems to study DNA condensation/compaction, in later parts, I highlight recent experimental methodologies to address the effects of macromolecular crowding and nanoscale and microscale confinements on DNA conformation dynamics. All the studies are discussed in the light of their relevance to DNA behavior in living cells, and future prospects of the field are outlined.

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1. Introduction

In a living cell, genomic DNA has to be strongly compacted to be accommodated within a confinement of micrometer size; therefore, the problem of DNA condensation (also referred to as "DNA folding" or "DNA compaction" for a single-molecule event) has attracted a considerable attention and has been rigorously studied for several decades. Experimental and theoretical studies on DNA condensation began in early 1970s of the past century. Since then a broad variety of experimental techniques was utilized to understand physical principles underlying DNA condensation and factors controlling DNA condensation *in vivo* and *in vitro*. The timeline in Fig. 1 shows the appearance of various *in vitro* experimental model systems aimed to make clear DNA packaging in cells. Most of early studies focused on DNA phase behavior in solutions of polyamines and other cationic chemicals. Meanwhile, studies on DNA condensation in concentrated solutions of neutral macromolecules and salt were initiated to address the effect of molecular crowding in cell.

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http://dx.doi.org/10.1016/j.cis.2016.02.005
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Please cite this article as: Zinchenko A, DNA conformational behavior and compaction in biomimetic systems: Toward better understanding of DNA packaging in cell, Adv Colloid Interface Sci (2016), http://dx.doi.org/10.1016/j.cis.2016.02.005

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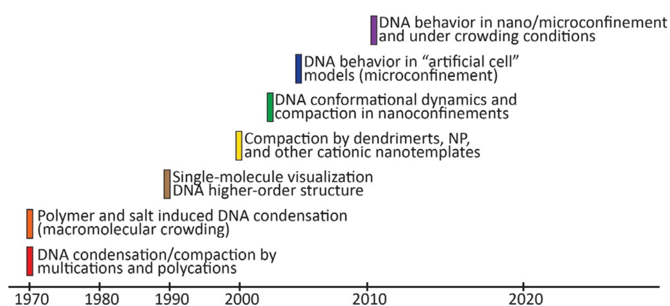

Fig. 1. Timeline (not to scale) of studies in the field of DNA condensation.

The progress in development of microscopic techniques in 1990s made possible single-molecule visualization of DNA conformational dynamics and folding/unfolding transitions and a more accurate interpretation of DNA compaction phenomenon.

However, in order to construct a more realistic experimental systems to model DNA behavior in the real cell, additional factors relevant to intercellular environment (Fig. 2) must be taken into account. The crucial ones are the following: (i) the presence of DNA condensing species interacting with negatively charged DNA predominantly by electrostatic mechanism, (ii) the presence of high concentrations of low-molecular weight electrolytes such as NaCl and $MgCl_2$ in solution, (iii) macromolecular crowding, and (iv) cell-sized microconfinement, in which DNA is placed. Ideally, all these factors should be considered simultaneously in a single experimental system; however, due to its obvious complexity, experimental design of such sophisticated system is a big challenge. During the past decade, along with new important experimental findings in (iii) and (iv) directions, there was a number of attempts to investigate the combined effect of two, three, or even four of above factors on DNA conformational behavior in a single model system. In this review, following the timeline in Fig. 1, first, I briefly overview DNA condensation/compaction starting from pioneering studies. Earlier studies on DNA condensation/compaction are well reviewed in past literature; therefore, here I mainly provide references to the corresponding review articles. In the later parts, I discuss recent progress in the analysis of the combined effect of all factors (i)–(iv) on DNA behavior. It should be mentioned that length of genomic DNA in cells is very long; therefore, I limit this review to studies focused on high-order structure of long DNA molecules of length exceeding hundreds of kilobase pairs unless otherwise mentioned.

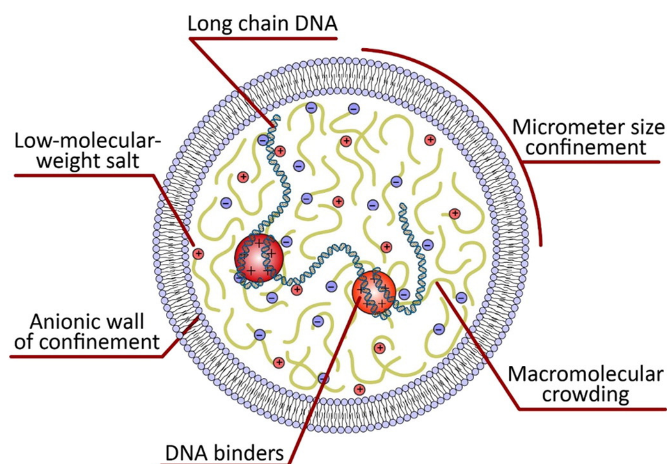

Fig. 2. Artificial cell model showing the complexity of an experimental system simultaneously taking into account the micrometer size of DNA confinement and the confinement wall effects, the crowded environment inside the confinement, the interaction of DNA with various types of cationic binders, and the presence of high concentrations of surrounded ions.

2. Compaction of DNA by positively charged molecules and colloids

In cells, condensation of negatively charged DNA is assisted by its interaction with cationic species of various charge and structure [1]. Earliest experimental *in vitro* models of DNA compaction utilized multivalent cations such as organic polyamines (spermine, spermidine, etc.) or cationic transition metal complexes (hexamine cobalt) [2,3]. DNA compaction was shown to occur as a result of neutralization of anionic charges on DNA macromolecule [4,5], which is largely promoted by ion correlation effect, i.e., attraction between like-charged DNA segments mediated by multivalent cations [6,7]. At the point of 89–90% neutralization/screening of the DNA charge, short range attractive forces overcome residual Coulombic repulsion between DNA segments resulting in DNA collapse [2,8]. Importantly, calorimetry studies demonstrated that binding of multivalent cations to DNA and subsequent DNA condensation are driven exclusively by the entropy contribution associated with the release of monovalent cations from DNA [9,10].

Experimentally, the compaction of DNA was studied as either DNA phase separation, i.e., precipitation of DNA from solution, or as a transition from an elongated state to a very compact globule state at the level of single DNA molecule (Fig. 3). Mono- and divalent cations do not induce DNA condensation in aqueous solutions because they are unable to sufficiently neutralize DNA charge and at least +3 charge on DNA compaction agent is required to induce DNA collapse [5]. Ion-exchange between monovalent and multivalent cations during DNA compaction contributes to stabilization of DNA compact state through an increase of translation entropy due to release of a large number of

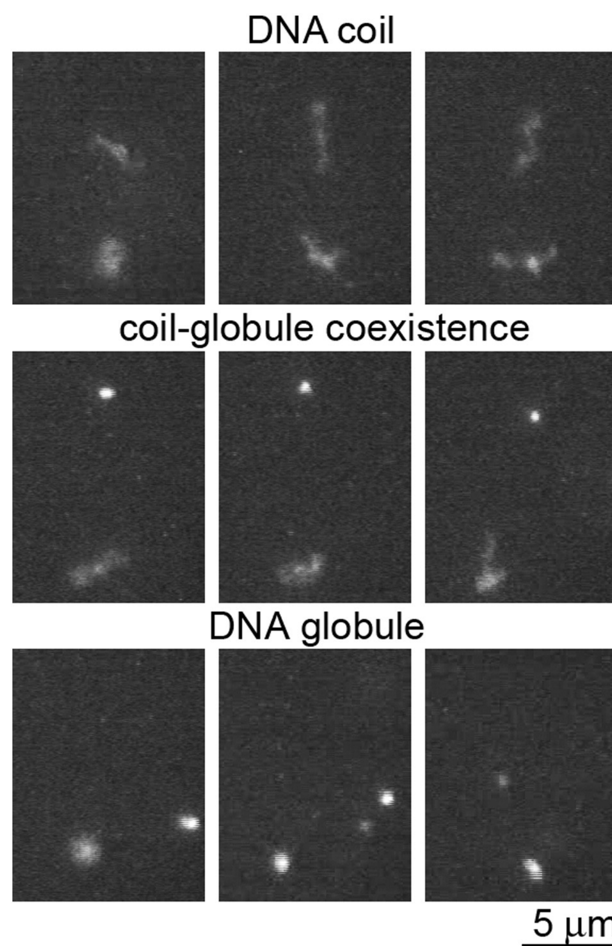

Fig. 3. Single-molecule observation of T4 DNA (165 kbp, ca. 60 μm contour length) compaction by spermine. Representative fluorescence microscopy images of dye-labeled T4 DNA molecules in coil, globule, and coil-globule coexistence conformational states.

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