

# Effects of Macromolecular Crowding on Structure of DNA



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Received:  August 01, 2018, 2018; Published:  August 09, 2018

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## Introduction

Biomacromolecules such as DNA, RNA, and proteins occupy 20 to 30% of the cell volume or even up to 40% [1-3]. The impenetrability of macromolecules greatly reduces the real activity space of any macromolecule, forming a cellular “macromolecule crowded environment” [4]. Macromolecular crowding effect significantly changes the activity coefficient of solute molecules in cells, which seriously affects the biochemical reaction rate and reaction progress [5-7]. The intracellular macromolecular environment has biophysical and chemical effects on the function and structure of DNA. It also plays an important role in the biological reactions involving DNA, such as increasing the bonding between DNA polymerase and DNA, promoting replication of DNA, increasing the efficiency of DNA hybridization, and accelerating the hydrolysis of DNA by nucleases [8,9].

## Effects on DNA Primary Structure

In an earlier study, Lerman [10] studied the effects of crowded environments on the phase behavior of DNA by mixing high concentrations of neutral polymers such as PEG and salts into the DNA. In a 10% volume fraction of neutral polymer and 0.3M NaCl solution, DNA collapsed into very compact particles. The squeezing is because DNA is insoluble in the neutral polymer and the depletion gravitation between DNA fragments contracts DNA into spheres. The high concentration of the salt solution effectively inhibits the static charge of the DNA and promotes its contraction. Hou [11] developed a variety of techniques, such as fluorescence correlation spectroscopy, dynamic light scattering and fluorescence analysis focusing on the premise of the formation of DNA nanoparticles. He found that in more than 25% concentration PEG 6K solution, macromolecular crowding environment promotes the formation of DNA nanoparticles which have a size of several hundred nanometers. Plasmid DNA (2686 bp) and double-stranded or single-stranded DNA fragments (66bp/NT) can form nanoparticles owing to the depletion effect of macromolecular crowding environment.

Anatoly [12] designed an experimental chromatin model system in vitro reconstructed by T4 DNA (about 166 kbp) and histone

octamers to investigate the single molecule compaction of the megabase-sized fibers under the effect of crowding environment. He observed that DNA and chromatin were compacted under considerable conditions in the presence of poly (ethylene glycol) and Na<sup>+</sup> or Mg<sup>2+</sup> salts and compared with K<sup>+</sup>, a more effective and significant chromatin compaction was observed in the presence of Na<sup>+</sup>. The compaction mechanism changes from the first phase transition of DNA to the continuous folding of the size of the mega base chromatin fiber. At monomolecular level, the behavior of DNA in a multivalent cation solution is similar to that in a neutral polymer solution, from a slender line to a compact sphere.

When the volume fraction of the polymer is constant, the longer the chain length of the neutral polymer, the larger the volume exclusion effect and the stronger the compacting effect. At the same time, the higher the salt concentration, the higher degree of the neutralization of negatively charged DNA, which resulting in strong compact effect. It is observed that the length of DNA chain is prolonged, and the fluidity of DNA is drastically decreased before the compaction of DNA in the dextran solution. The reason for this phenomenon is difficult to explain so far and can only be interpreted as the complex effect such as entropy reduction and the mobility of crowding agents [13]. In a high concentration of dextran solution, the transcriptional activity of DNA is completely inhibited after compacting into a sphere [14].

## Effects on DNA Secondary Structure

The crowded environment near DNA molecules not only has a strong influence on the conformational behavior of DNA, but also has a profound effect on the secondary structure of DNA. The stability of the double helix structure of DNA in a macromolecular environment was investigated by testing the melting temperature of DNA as it was untwisted from a double helix to two single strands of DNA. In most studies, the addition of crowded agents results in an increase in the stability and melting point of DNA secondary [15] and tertiary structure [16]. Anionic crowding agents have better stability than neutral crowding agents, probably because

additional charge enhances the volume exclusion effect. At the same time, some papers have pointed out that the DNA double helix structure decreases stability in the presence of PEG and anion particles [17]. This is because the rate of strand exchange of DNA duplexes in PEG solution increases rapidly, resulting in acceleration of DNA denaturation [18]. The effect of crowded environments on the stability of DNA double strands is attributed to the interaction of many factors such as reduced water activity, the behavior of counterions, and destruction of hydrogen bonds between DNA duplexes. The effects of each factor vary in a particular system, but all depend on the length of the DNA, the size and charge of the crowded agents and the ionic strength [19].

## Conclusion

Although it is certain that DNA tends to contract into a compact conformation in crowding environment, there are still lots of complicated behaviors and mechanisms remaining unsolved. The crowding effect is as much important as the other physiological factors such as pH and ionic strength [20]. Therefore, the study on the structure, properties, function and interaction of macromolecules in the crowded environment and the mechanism research of crowding effect on the cellular biochemical processes are of great theoretical significance and have a medical practical value for deepening the understanding of the functions of living organisms and life phenomena.

## Acknowledgment

This work is supported by the National Natural Science Foundation of China (Project No. 21476072) and the Fundamental Research Funds for the Central Universities.


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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2018.07.001545

YZ Shang. Biomed J Sci & Tech Res

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