

Electrical induction hypothesis to explain Enhancer-Promoter Communication.

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Abstract

The steps of the DNA replication process remains to be clarified. Transcription factors are supposed to find their specific binding-sequence driven by epigenetic modifications and GpC islands. But then how can the replication machinery be able to find the promoters of exactly the genes that the cell needs to transcribe in that moment? Here we hypothesize a role of DNA conductance and electrical induction to give an explanation to this unsolved problem. Our hypothesis goes in accordance with the fact that many authors identified 3D loops in the genomes.

Introduction

Enhancers (E) are short (20-400 bp) DNA sequences that can activate transcription from target promoters (P) in trans and over variable distances (more than 100 kb) (Bondarenko, Liu et al. 2003).

Enhancers operate in pro- and eukaryotes; in the majority of cases action of Es involves direct E-P interaction through proteins bound at the E and P, accompanied by formation of intervening chromatin loop (Bondarenko, Liu et al. 2003). In a review (Kulaeva, Nizovtseva et al. 2012), Kulaeva and colleagues focus on mechanistic aspects of enhancer action. Despite their analysis, the enhancer field remains driven by the concept of recruiting (Ptashne 1986). During recruiting, an activator protein increases local concentration of RNA polymerase, in the vicinity of its binding site. But, even if a protein complex was recruited to enhancer, its concentration at the target would not necessarily be increased because the E/P do not typically co-localize. Furthermore, they analyze the hypothetical mechanisms of long-range EPC (enhancer-promoter communication) involving histone N-tails. Genomic studies identified specific "signatures" (histone modifications, associated proteins and conserved non-coding elements (CNEs)). Conserved non-coding elements (CNEs) role in cis regulation had been described by Nelson et al., 2013 (Nelson and Wardle 2013). However, despite having the entire sequence of the genome, very little has been understood about three-dimensional chromosome conformation beyond the scale of the nucleosome. But, recent advances in molecular biology and computational analysis have lent insight into chromatin interactions on a larger scale. Chromosome conformation capture (3C) methodology was developed to study spatial organization of long genomic regions in living cells. It is important to estimate the ligation frequencies using the real-time PCR (Gavrilov, Eivazova et al. 2009).

The three-dimensional conformation of chromosomes in the nucleus is important for many cellular processes, including the regulation of gene expression, DNA replication, and chromatin structure (Cremer and Cremer 2001).

The technique of chromosome conformation capture (3C) evaluates long-range interactions between specific pairs of loci by using spatially constrained ligation followed by locus-specific polymerase chain reaction (Dekker, Rippe et al. 2002).

While useful for specific loci of interest, 3C has very limited throughput.

A modification of 3C, circularized chromosome conformation capture (4C), has the advantage that the sequence of only one site of interest needs to be known. However this method is limited in terms of throughput since only one input sequence can be used per experiment.

An additional method with slightly higher throughput, carbon copy chromosome conformation capture (5C) expands on 3C by allowing parallel analysis of the interactions between many selected loci (Dostie,

Richmond et al. 2006). Very recently, a novel method, termed Hi-C, has been developed to overcome these difficulties and assess chromosome conformation across the entire genome at a scale of 1Mb (Lieberman-Aiden, van Berkum et al. 2009) visualized as plots. These techniques lead to the identification of topologically associating domains (TADs) and insulators. TADs are stable units of replication-timing regulation (Pope, Ryba et al. 2014). Replication timing is cell-type-specific with in units of 400–800 kilobases ('replication domains') that appear to confine long-range effects of chromosome rearrangements. They reconcile cell-type-specific sub-nuclear compartmentalization and replication timing with developmentally stable structural domains.

Individual domains are divided by boundaries established through a balance between condensation and decondensation of chromatin. Alternatively, specific DNA sequences and associated proteins might have the role of establishing fixed boundaries (West, Gaszner et al. 2002). "Insulator" is the name given to a class of DNA sequence elements that possess a common ability to protect genes from inappropriate signals emanating from their surrounding environment. There are two mechanisms of action: enhancer blocking occurs if the insulator is situated between the enhancer and the promoter, whereas a second type creates a barrier against the spread of heterochromatin (Gaszner and Felsenfeld 2006).

Discussion

It has been recently demonstrated that DNA is able to transport electrons: experiments reveal that resistivity is comparable to those of conducting polymers, and indicate that DNA transports electrical current as efficiently as a good semiconductor. Direct measurements of electrical current as a function of the potential applied across a few DNA molecules associated into single ropes at least 600 nm long (Fink and Schonenberger 1999). Computer modeling studies suggest that the average distance between linearly separated DNA regions could be considerably decreased on supercoiled DNA (Vologodskii and Cozzarelli 1996). Indeed, DNA supercoiling greatly facilitates EPC over a large, but not over a short (<1 kb) distance through a mechanism that involves a global change of DNA conformation. Computer simulations and experimental studies suggest that DNA supercoiling results in formation of DNA "branches" and thus increases the probability of juxtaposition between linearly separated DNA sites, provided that DNA branches are dynamic structures (Kulaeva, Nizovtseva et al. 2012).

Heterochromatin structure recall to mind electrical coil bobbins. Here we propose an attempt to reconcile DNA looping and transcription.

Our hypothesis provides for a binding of the transcription factor (TF) that allows the creation of an electric current (maybe through the Zn-fingers or similar domains). The electrons flow through DNA (negatively charged) and induce a conformational change in the histones (positively charged). Electrical induction (possibly in histone alpha-helices) could be the phenomenon that causes chromatin disassembly so that the polymerase is now free to bind the promoter (Fig. 1A). Moreover, the turn created (Fig. 1B) might keep at distance others TFs and positively-charged proteins like histones.

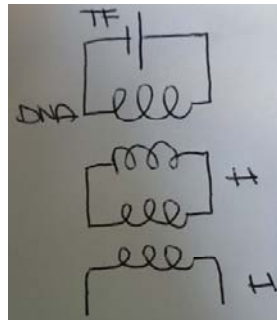
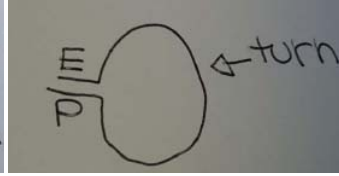
A.**B.**

Fig.1. A: Possible circuits and electrical induction between DNA coil bobbins and histone alpha-helices. B: The turn created by the binding of proteins (TF: transcription factor, H: histone, E: enhancer, P: promoter)

Our hypothesis goes in accordance with the fact that in Rao et al., 2014 (Rao, Huntley et al. 2014) the authors use in situ Hi-C to probe the 3D architecture of genomes. Furthermore, the TF could find its specific binding-sequence driven by epigenetic modifications and GpC islands, but then how can the replication machinery be able to find the promoters of exactly the genes that the cell needs to transcribe in that moment? We had hypothesized a pivotal role of DNA conductance and electrical induction in giving an explanation to this unsolved problem.

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