DNA Dynamics and Biological Function

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The DNA molecule is the main source of information in living organisms on our planet. DNA contains and transmits vital information from the nucleus to the cell body, in a process known as transcription, which is initiated at specific DNA promoter sequences. Similarly, the DNA molecule is able to self-replicate, and thus to reproduce itself in a process called replication. DNA can also change its structure by incorporating parts of helical molecules in a process known as recombination. These three processes are at the heart of biological functions. An important point is that all of them require access to the genetic code, which is protectively embedded in the hydrophobic center of the DNA double helix. In order for this information to be accessed, the DNA nucleotides must be physically exposed by locally opening the double helix of the molecule.

Thermally induced local transient openings (breathing) of the DNA are well-documented phenomena [1] that can result in DNA non-canonical structures that are significantly different from the equilibrium Watson and Crick helix. It is important to note that this breathing is present in all DNA molecules as a result of the thermal energy and thermal fluctuations of the water in the cell. In other words, specific "soft" segments along the DNA are unceasingly a subject of transient destabilizations, or local melting, by the available thermal energy in the system. Although, this DNA breathing has been recognized for decades, it was commonly believed that the functional properties of DNA were determined exclusively by the composition of the nucleotides–that is, the gene sequence of the molecule. However, it is now widely accepted that the dynamical conformational changes of DNA play a key role in biological function. The tendency for DNA promoters to possess enhanced transient local openings (bubbles) is independent of any DNA-protein interactions or regulation, and is therefore a property of the DNA sequence itself, although influenced by environmental factors. Hence, the sequence dependence of DNA bubbles is not simply a matter of sequence identity, but also of the interplay of interactions, in determining the physical properties of DNA. It is also interesting to note that a significant tendency to open is found at many of the known transcription factor binding sites, suggesting a mechanism of protein-DNA recognition based not only on sequence, but on the formation of the transient localized DNA openings.

Our work establishes that transcriptional start sites (TSS) and transcription-factor-binding sites (TFBS) possess enhanced local DNA breathing dynamics associated with nonlinear vibrational "hotspots" [2-4]. Importantly, their dynamical patterns are strongly interconnected with the function of the TSS or TFBS. We have demonstrated this interconnection using computer simulations to identify the hotspots of several mammalian TSSs and TFBSs, and experimentally by: (1) designing DNA single-point mutations to silence TSS dynamics, which led to a concomitant suppressed transcription without affected transcription-factor binding [2] (Fig. 1), and (2) introducing an artificial mismatch opening at a TSS site, which led to bidirectional transcription initiation in the absence of basal transcription factors [4]. Based on this work, it is becoming clear that a methodology to influence these breathing dynamics may help enable external control of biological function. Because these dynamics are controlled mainly by the hydrogen bonding within the DNA molecule and thus occur at the picosecond time scale, a primary candidate for exercising external control is electromagnetic fields in the far-infrared range of the spectrum.

We used our modeling framework to investigate the influence of terahertz (THz) radiation on DNA breathing and demonstrated [5] that, at sufficient exposure, DNA bubbles can appear through a nonlinear resonance mechanism, even at low-power THz fields (Fig. 2). Such bubble formations required prolonged THz exposure but may have a direct effect on transcription, replication, and DNA-protein binding, thus providing a connection between THz radiation and biological function. Recent experiments performed by us and others demonstrated that specific THz radiation conditions can indeed lead to modified gene expression profiles (Fig. 3), and gene-specific activation and repression in mouse stem cells [6].

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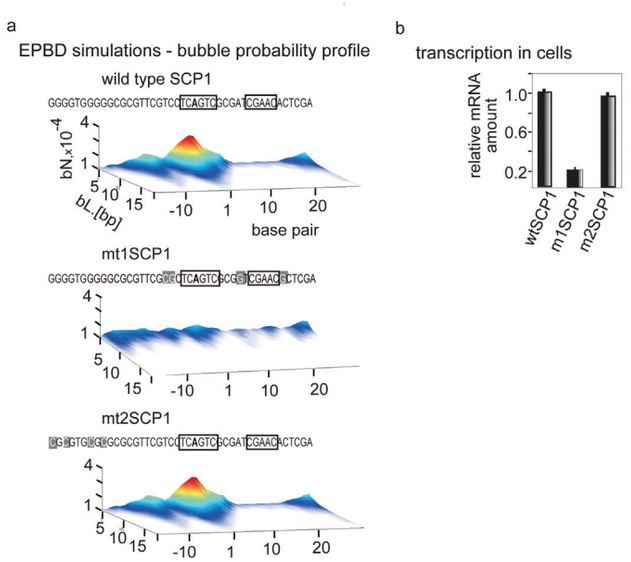

Fig. 1. Theoretically designed mutations that change the bubble probability profile and transcriptional activity while preserving TFIID complex formation at the SCP1 promoter. (A) Bubble probability profiles of the wild-type SCP1 promoter (wtSCP1), m1SCP1, and m2SCP1 mutant variants designed to silence transcription activity without affecting protein-binding sites. The probability (z-axis) for the formation of bubbles of amplitude >3.5 Å with length L (y-axis) beginning at a given nucleotide position (x-axis) relative to the TSS ("+1"). The wtSCP1, m1SCP1, and m2SCP1 sequences are shown at the top. Mutated residues are indicated with gray boxes. Protein-binding sites are indicated with black frames. (B) Transient cell transfection experiments were carried out to measure wtSCP1, m1SCP1, and m2SCP1 promoter activity. Data are expressed as fold induction relative to wtSCP1 mRNA level (on the vertical). Figure is adapted from [2].

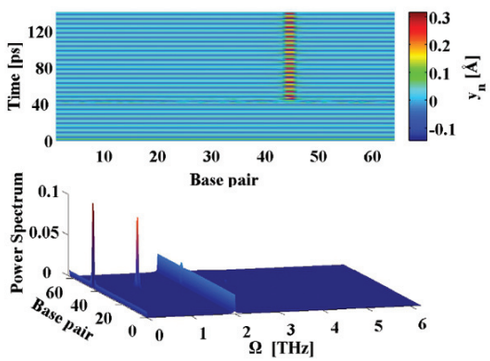

Fig. 2. Breather formation in a model of homogenous DNA under exposure to a THz field (Ω = 2.00 THz). The upper panel shows the evolution of the breather. The lower panel shows the power spectrum of the breather motion, and demonstrates that the frequency of the vibrations of the resonance breather is mainly Ω/2 (i.e., a period-doubling transition has occurred) as expected from our analysis. Adapted from [5].

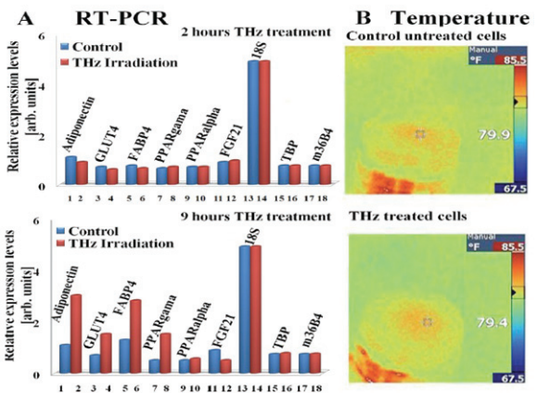

Fig. 3. Differential gene expression in response to broadband THz radiation normalized to ribosomal 18S genes. (A) 2 hours radiation and 9 hours radiation of mouse stem cells. The experimental results are consistent between three independent real-time RT-PCR measurements in duplicates. (B) The temperature was monitored using an IR detector, and separately using thermo-sensors glued to the outside of the petri dish lids. The temperature (in degrees Fahrenheit) at the end of irradiation is shown for the control and the irradiated cells. Adapted from [6].

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