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Self-Assembly of an Oligodeoxyribonucleotide Harboring the Estrogen Response Element in the Presence of Polyamines: Ionic, Structural, and DNA Sequence Specificity Effects

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Estrogenic regulation of gene expression is mediated by the binding of the hormone to its specific receptor, estrogen receptor (ER), which undergoes structural and conformational alterations to recognize specific DNA sequences, estrogen response element (ERE), in responsive genes to trigger a series of events culminating in the transcription of genes. Polyamines are ubiquitous cellular cations that are important for cell growth and differentiation, and have been shown to participate in estrogenic regulation of gene expression. Polyamine-mediated DNA condensation/aggregation has been studied to understand the ionic and structural requirements for the compaction of DNA. DNA condensation/decondensation may also play a role in transcription and replication. We studied the aggregation of a 38-mer oligonucleotide duplex (ODN) in the presence of natural and synthetic polyamines under different ionic conditions (NaCl, KCl, and K glutamate). Our results showed that an ODN harboring the consensus ERE (ODN1) was 2-fold more susceptible to precipitation by spermine compared to ODN2 containing scrambled sequences, or a mutant ODN(ODN3). The nature of the monovalent cations ( $\text{Na}^+$  vs  $\text{K}^+$ ), and anions ( $\text{Cl}^-$  vs glutamate) also played an important role in the efficacy of a polyamine to precipitate ODNs: potassium glutamate being the least effective in suppressing the ability of spermine to precipitate ODNs. The concentration of polyamines required for precipitating the ODNs increased with monovalent ion concentration in the buffer.

With ODN1, a plot of  $\log[\text{spermine}^{4+}]$  at the 50% precipitation concentrations against  $\log[\text{Na}^+/\text{K}^+]$  yielded a straight line, with a slope of  $1.8 \pm 0.18$ , a value comparable to that predicted by the counterion condensation theory (1.85). We also observed significant structural specificity effects of spermine and its analogues  $[\text{NH}_2(\text{CH}_2)_3\text{NH}(\text{CH}_2)_n\text{NH}(\text{CH}_2)_3\text{NH}_2]$ , where  $n = 2-9$ ;  $n = 4$  for spermine] on aggregating the ODN1. These results demonstrate DNA sequence and polyamine structural specificity effects on the aggregation of ODNs, and suggest that the gene regulatory function of ERE may be linked to its ability to undergo facile condensation/decondensation in the presence of biological cations, such as polyamines.