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Article

Site-Specific Topoisomerase I-Mediated DNA Cleavage Induced by Nogalamycin: A Potential Role of Ligand-Induced DNA Bending at a Distal Site†

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Abstract

Many DNA binding ligands (e.g., nogalamycin, actinomycin D, terbenzimidazoles, indolocarbazoles, nitidine, and coralyne) and various types of DNA lesions (e.g., UV dimers, DNA mismatches, and abasic sites) are known to stimulate topoisomerase I-mediated DNA cleavage. However, the mechanism(s) by which these covalent and noncovalent DNA interactions stimulate topoisomerase I-mediated DNA cleavage remains unclear. Using nogalamycin as a model, we have studied the mechanism of ligand-induced topoisomerase I-mediated DNA cleavage. We show by both mutational and DNA footprinting analyses that the binding of nogalamycin to an upstream site (from position −6 to −3) can induce highly specific topoisomerase I-mediated DNA cleavage. Substitution of this nogalamycin binding site with a DNA bending sequence (A_5) stimulated topoisomerase I-mediated DNA at the same site in the absence of nogalamycin. Replacement of the A_5 sequence with a disrupted DNA bending sequence (A_2TA_2) significantly reduced the level of topoisomerase I-mediated DNA cleavage. These results, together with the known DNA bending property of nogalamycin, suggest that the nogalamycin−DNA complex may provide a DNA structural bend to stimulate topoisomerase I-mediated DNA cleavage.

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