Cooperativity and Competition in the Binding of Intercalators and Groove Binders to DNA

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Abstract Id: ***444*** *Submitted:* ***February 21, 2019*** *Event:* ***Conference for Undergraduate Research at FIU 2019*** *Topic:* ***Biochemistry***

Both DNA intercalating ligands such as psoralens and DNA groove binding ligands such as heterocyclic diamidines have been shown to alter the activity of restriction endonucleases if bound at or near the restriction enzyme reaction site. When two agents have binding sites near a particular restriction enzyme site, the possibility arises that each may affect the binding and binding consequences of the other. We have examined this by examining the effects of heterocyclic diamidine mixtures or of diamidine/psoralen mixtures or of heterocyclic diamidine/Co+2 mixtures upon the reactivity of several restriction enzymes on phix174RF DNA. For example, with the restriction enzyme Mlu I [ACGCGT], separately the diamidines DB 293 and DB818 produce inhibition of cleavage. The combination produces enhanced cleavage – which implies a DNA structural alteration. This suggests that these agents, while both groove binders, bind differently and when together, perhaps cooperatively. With Ava II [GGACC], DB818 alone produces enhanced cleavage and DB293 produces inhibited cleavage. The combination produces inhibited cleavage. 8-methoxypsoralen, an intercalator, alone produces inhibition of Mlu I cleavage. The mixture of 8-methoxypsoralen and DB818 results in enhanced cleavage. Alone, Co+2 does not affect reactivity of the restriction enzymes examined. DB293 alone enhances cleavage by Stu I [AGGCCT]. The combination of DB293 and Co+2 produces inhibited cleavage by Stu I. These results and the results with other restriction enzymes cleaving at different sequences suggest that the agents examined affect the structure of DNA upon binding and thus affect the binding of other agents to these locations.