Sequence Context Effects on the Structural Dynamics of Abasic Site Derived DNA Interstrand Crosslinks

Nathania Takyi and Stacey D. Wetmore

Department of Chemistry, University of Lethbridge, AB, Email: nathania.takyi@uleth.ca

DNA controls the development and tissue function in complex multicellular organisms. However, cellular function can be affected by DNA damage. One common form of DNA damage is apurininc/apyrimidinic (Ap) sites, which are nucleotides that lack a nucleobase. Ap sites can form due to incomplete base excision repair or spontaneous depurination, which can be formed following the interaction of DNA with metabolites. *In vivo*, Ap sites exist as an equilibrium between a ring-closed form and a ring-open form that bears an aldehyde at C1′. In the aldehyde derivative, C1′ can be attacked by a nearby nucleobase, which results in an interstrand crosslink (ICL). If left unrepaired, these crosslinks can prevent DNA replication and transcription, and can result in cell death.

To understand the implications of these relatively newly identified type of ICLs, it is integral to uncover the conditions under which they are most likely to arise. In this light, sequence context has been an area of great interest. For example, an ICL between N6 of adenine and C1′ of an Ap site (dA–Ap) has been observed to predominantly form when a nucleophilic adenine is present in the 5′ direction in the opposing strand, yet will not form when the adenine is complementary to the Ap site. Furthermore, *in vitro* experimental studies have revealed that the formation of a dA–Ap crosslink is less favourable in the 5′-AAC-3′3′-TXG-5′ (X = Ap site) sequence (15% yield) than in the 5′-AAG-3′3′-TXC-5′ sequence (70% yield). However, the reasons for this preferential formation of the dA–Ap lesions are currently unknown.

In order to gain a better understanding of the role that sequence context plays in the formation of Ap-derived interstrand crosslinks, molecular dynamics (MD) simulations (AMBEROL15) were performed on DNA duplexes containing the dA–Ap crosslink in two sequence contexts (5′-AAC-3′3′-TXG-5′ and 5′-AAG-3′3′-TXC-5′, X = Ap site). The effect of sequence context on the structural dynamics and the nonbonded interactions surrounding the lesion site of DNA helices containing all possible dA–Ap crosslinks was determined. Together, this data provides a structural explanation for the differential formation of dA–Ap interstrand crosslinks. The knowledge obtained from this study can be used in the development and fine tuning of therapeutics as inducing ICLs is a common chemotherapeutic technique.