Chemical modifications to the CGG/CGG triad by synthetic naphthyridine derivatives

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Abnormal expansion of DNA CGG trinucleotide repeat, located in the 5' untranslated region of the FMR1 gene on X chromosome, is closely associated with Fragile X syndrome (FXS).[1] Identification of potential small molecules capable to disrupt the continuous CGG traid is considered as a promising strategy for disease regulation or treatment.

Given the strong recognition of naphthyridine carbamate dimer (NCD) to G-G mismatch (Fig. a)[2,3] and alkylation property of epoxy group to DNA base(s)[4], we herein designed and synthesized novel naphthyridine derivatives, NCD-epoxy (Fig. b), targeting DNA CGG repeat sequences. Upon treatment with DNA CGG/CGG mismatch, preferential binding of NCD fragment in NCD-epoxy offers spatial opportunity for alkylation reaction between epoxy group and CGG unit. The flipped out cytosines induced by NCD binding may have higher reactivity than base-paired cytosines, which are expected to be the alkylated sites along with the reactive guanine base(s).

Increasing melting temperature of DNA sequence confirmed the binding and stabilization effect of NCD-epoxy to CGG/CGG mismatch. The production of DNA alkylated adducts by epoxy group were also revealed by high-performance liquid chromatography (HPLC) method. Identification of the alkylated products by chemical methods cleaving glycosidic bonds at alkylation sites is in progress.

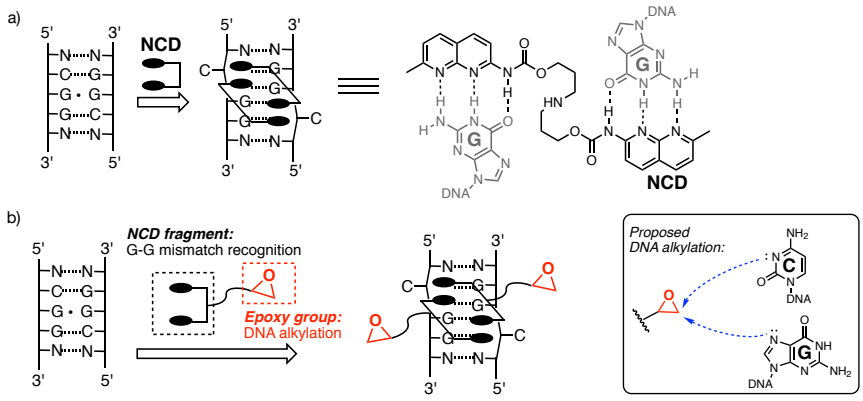

Fig. a) Proposed binding pattern between NCD and G-G mismatch. b) Possible binding behavior of NCD-epoxy with G-G mismatch.

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