Modulation of APOBEC-catalyzed cytosine deamination by a small molecule binding to DNA

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Development of therapeutic strategies for genetic diseases has been a challenge for many years. Repeat expansion disorders are a class of genetic diseases, which are caused by the expansion of various repeat sequences in DNA. The majority of repeat expansion disorders are caused by trinucleotide repeats. For instance, expansion of CGG repeat sequences on the X chromosome is associated with Fragile X syndrome (FXS) characterized by intellectual disability and autism. The aberrant expansion of CGG repeats (> 200 repeats) in the 5'-untranslated region of the FMR1 gene causes transcriptional silencing of the FMR1 gene and results in the deficiency of FMR1 protein that is essential for the normal development of neurons. Since the severity of symptoms generally collates with the repeat length, interrupting aberrant expansion repeat to below the pathogenetic threshold is a promising strategy for the treatment of repeat expansion disorders.

Naphthyridine carbamate dimer (NCD) is a mismatch binding small molecule, which has been reported from our laboratory. NCD selectively binds to CGG/CGG motif [1] in duplex DNA by forming hydrogen bonds with the guanines, while the cytosines are flipped out of the duplex due to NCD occupancy within the duplex DNA.

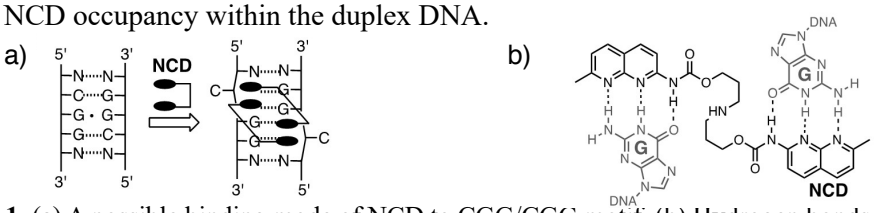

Figure 1. (a) A possible binding mode of NCD to CGG/CGG motif. (b) Hydrogen bonds between NCD and guanines.

Given the binding characteristics of NCD, we hypothesized that flipped-out cytosines might be susceptible to deamination by cytosine deaminases. APOBEC (apolipoprotein B mRNA editing catalytic polypeptide-like) proteins are a family of cytidine deaminase that converts cytosine (C) to uracil (U) on single-stranded DNA or RNA.[2] In this study, we investigated the effect of NCD binding to CGG repeat DNAs on in-vitro deamination of cytosines with APOBEC proteins.

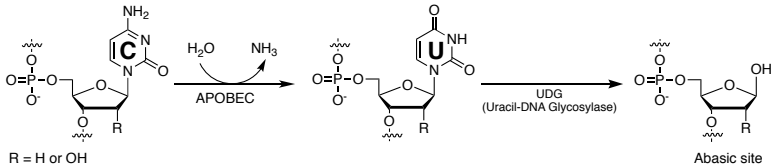

Figure 2. The cytosine deamination by APOBEC.

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