Elucidating the Recognition Mode of T-T Mismatches by Small Molecules as a Step Toward Drug Discovery in Myotonic Dystrophy

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Myotonic dystrophy is a debilitating genetic disorder wherein patients may exhibit a range of symptoms including cataracts, heart conduction defects, loss of muscle strength, and myotonia. The signature of the disorder is expanded trinucleotide CTG repeats in the 3′-untranslated region of the *DMPK* gene. Transcription results in the creation of toxic expanded RNA which sequesters RNA-binding proteins involved in mRNA splicing and this ultimately leads to the symptoms of the disease. The exact mechanism of CTG expansion is unknown but a replication-dependent model states that upon unwinding, CTG repeats form stable hairpins with T-T mismatches which lead to polymerase slippage and trinucleotide expansion. One suggested therapeutic approach is to reduce the rate of expansion or promote contraction with a small molecule agent.

While developing a structure-activity relationship of one promising CUG-selective small molecule, we discovered an analog that binds selectively to CTG sites in DNA. More importantly, in contrast to binding studies with RNA (CUG), experiments suggest a different binding mode for DNA (CTG) in which one of two thymines might not be directly involved upon ligand binding. Molecular dynamics (MD) simulations further suggest that a thymine residue is flipped-out of the duplex. Base flipping is often observed with DNA modifying and error repairing enzymes, suggesting the potential of the small molecule to signal error repair pathways, and or disrupt the CTG hairpin formation.