Selective chemical functionalization of $N^6$-methyladenine in DNA

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Selective chemical reactions on nucleobases have been key driving forces for the study of base modifications in DNA and RNA.[1] Methylation at adenine $N^6$ to form $N^6$-methyladenine ($N^6$mA) is one of the the most abundant modified bases in mammalian transcriptomes as well as in bacterial genomes. A growing number of studies suggest its presence and potential regulatory roles in the DNA of mammals including humans,[2,3] but the available methods for its detection are not always reliable.[4]

The aminomethyl group in $N^6$mA being a unique feature in eukaryotic genomes, we explored possibilities to chemoselectively functionalise $N^6$mA in DNA strands. We were inspired by the dioxygenases responsible for $N^6$mA demethylation in vivo, operating via hydrogen abstraction from the $N^6$-methyl group to form an intermediate ‘on-DNA’ radical species. Relying on a visible-light-mediated photoredox process to generate a hydrogen abstracting species as well as a radical acceptor, we were able to selectively form an ‘on-DNA’ radical at $N^6$mA and intercept this intermediate with the in-situ formed radical acceptor.[5]

We further developed an alkynylated probe for downstream functionalisation and demonstrated that we could biotinylate $N^6$mA in longer single-stranded and double-stranded DNA. This allowed us to enrich for $N^6$mA-containing DNA fragments from complex DNA mixtures. This work sets the base to further development for chemistry-based methods to map $N^6$mA in nucleic acid strands.