The Role of N6-methyladenosine (m^6A) RNA Methylation in the Hepatitis B Virus Life Cycle

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Abstract

N6-methyladenosine (m6A) RNA methylation most prevalently occurs in cellular and viral RNAs. Here, we investigated the m6A functions in the hepatitis B virus (HBV) life cycle. We identified a single m6A consensus motif at nucleotide position 1907. All HBV transcripts bear this motif at the 3′ end epsilon structure, but pregenome RNA (pgRNA) carries this motif twice, at 5′ and 3′ epsilon structures, owing to the terminal redundancy of sequences at its 5′ and 3′ end. Interestingly, m6A methylations differentially regulated the HBV life cycle dependent on its position. 3′ m6A modification reduced viral RNA stability, affecting corresponding viral protein expression, but 5′ m6A modification is essential for pgRNA encapsidation to synthesize viral DNA. Further, we found that HBV X (HBx) protein recruits host methyltransferases to nuclear HBV DNA to induce co-transcriptional m6A methylation. This study highlights the pivotal role of m6A methylation in the HBV life cycle.