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N6-methyladenosine modifications regulate hepatitis E virus infections

Inhalt

N6-methyladenosine (m6A) is the most prevalent cotranscriptional RNA modification in eukaryotes, regulated by m6A methyltransferases (writers), demethylases (erasers) and m6A-binding proteins (readers). Its role during hepatitis E virus (HEV) infection remains poorly understood. Therefore, we blocked METTL3 activity in inhibitor dose-response assays. METTL3 inhibitors STM2457, STM3006 and STC-15 reduced infection with EC50 values of 3.7, 1.2 and 5.4 μ M, respectively. These antiviral effects were confirmed in extrahepatic cells and primary human hepatocytes, where STM2457 demonstrated an 75% reduction at 25 μ M. Time-of-addition assays indicated that METTL3 primarily regulates the viral entry stage. Combining STM2457 with replication inhibitors Ribavirin or JNJ-9117 yielded additive antiviral effects. Interestingly, direct RNA Nanopore sequencing of HEV-transfected HepG2 cells treated either with STM2457 or DMSO detected no m6A sites on the HEV genome, suggesting that m6A instead regulates host-specific responses. Finally, co-treatment with the JAK/STAT inhibitor Baricitinib showed no differences compared to single treatment, indicating that METTL3 functions independently of the innate immune defense. In conclusion, our study identified m6A methylation as a component of HEV biology and suggests that it might be a promising target for antiviral interventions.

Keywords

Hepatitis E Virus, RNA modification, N6-methyladenosine, STM2457, METTL3

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Yes, I am a Junior Scientist.

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