A novel LNP/mRNA-based STING immunotherapy approach for chronic HBV infection

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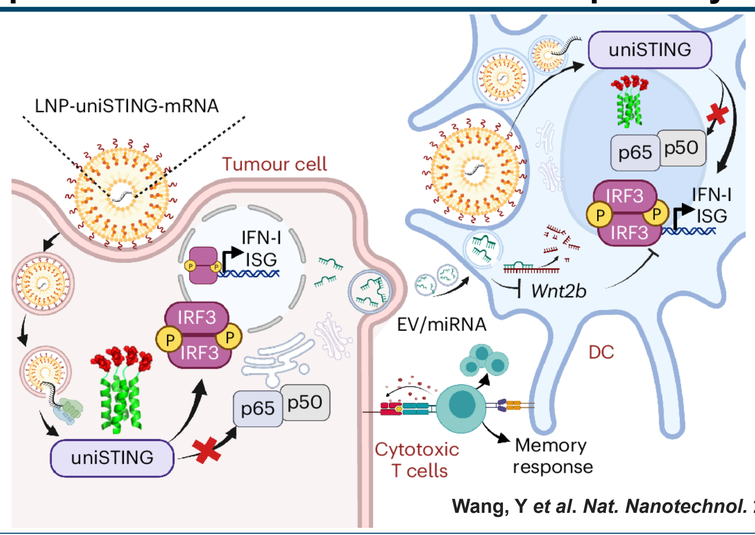
Background

In this study, we evaluated a novel universal STING mimic (**uniSTING**) formulated in lipid nanoparticles (LNPs) delivering mRNA encoding uniSTING. Upon expression, uniSTING self-assembles into tetrameric and higher-order polymeric structures with constitutive activity, preferentially activating the IRF3/IFN-I axis while minimizing NF-κB signaling. In vitro, uniSTING robustly reduced HBV cccDNA replication. In naïve mice, systemic delivery elicited strong serum IFN-β and ISG induction. Importantly, in a chronic HBV carrier mouse model, LNP/uniSTING administration led to sustained reductions in serum HBV DNA and HBsAg, together with the emergence of anti-HBs IgG and broad ISG expression. These findings indicate that uniSTING can overcome immune tolerance and elicit potent antiviral and humoral responses, highlighting its potential as a therapeutic strategy for chronic HBV infection.

Methods & Results

1. uniSTING boosts antitumor immunity via preferential activation of IRF3/IFN-I pathways



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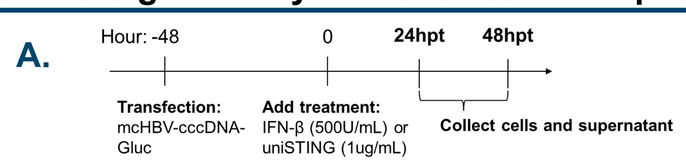
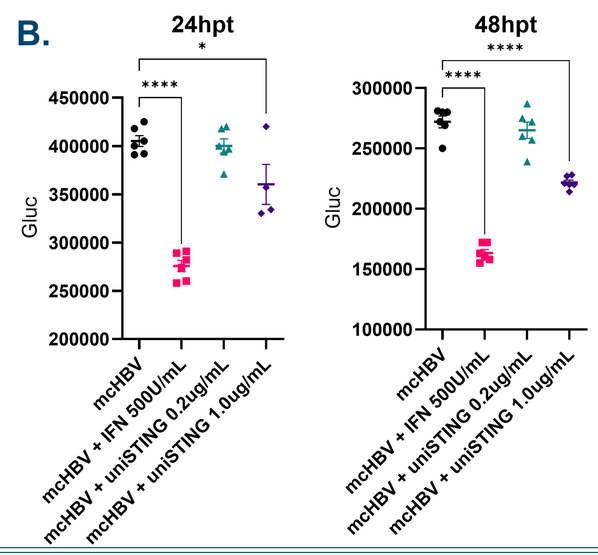
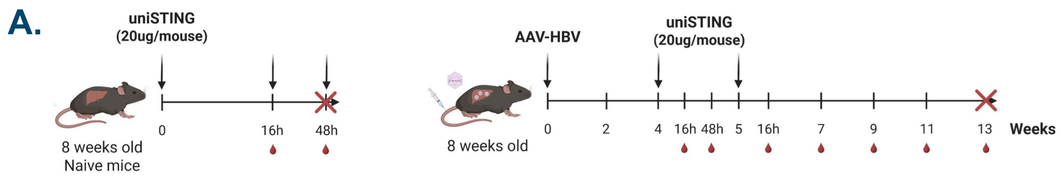
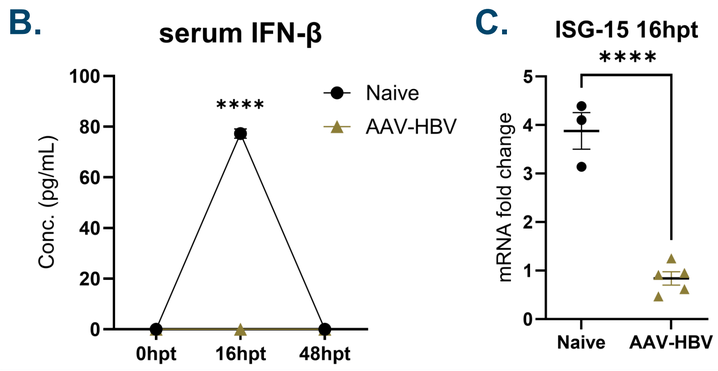
2. uniSTING significantly reduces cccDNA replication

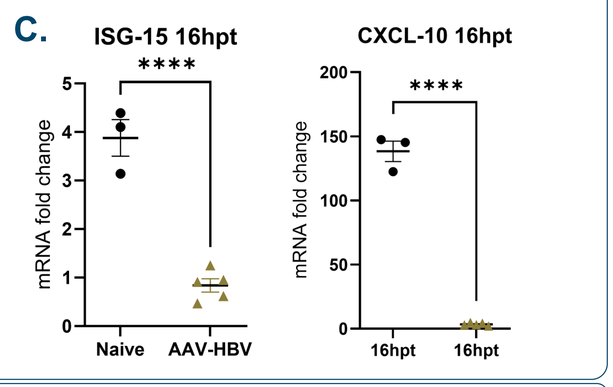




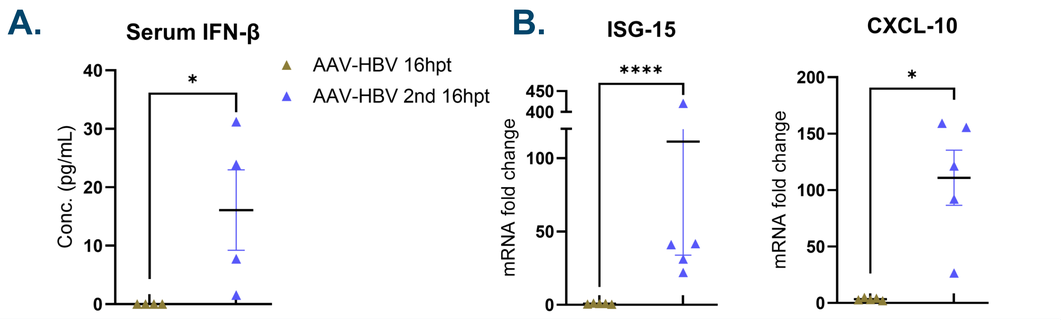
3. Impaired IFN-β induction by uniSTING in chronic HBV mice.



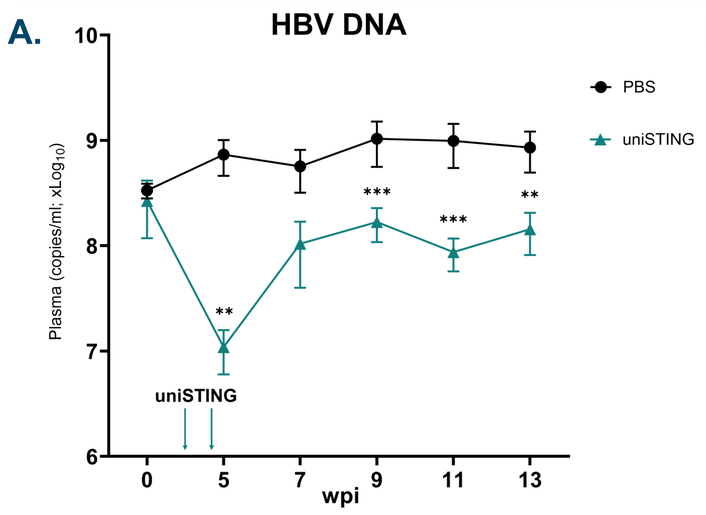


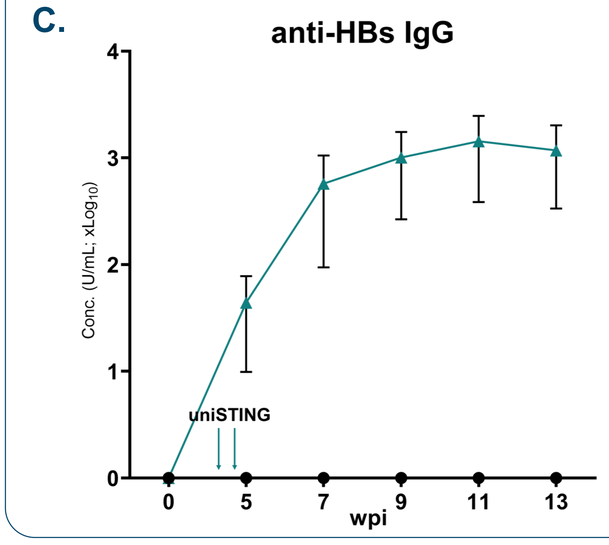


4. uniSTING induces IFN-β and ISG expression only after the second dose in chronic HBV mice.



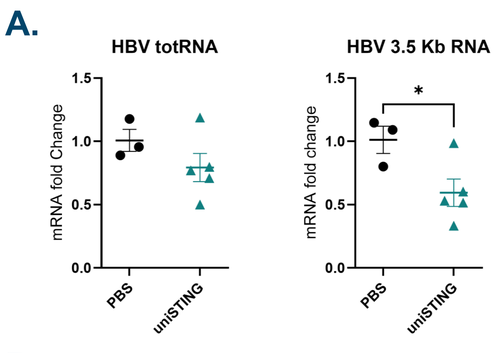
5. uniSTING treatment suppresses HBV replication and induces anti-HBs IgG production in chronic HBV mice.

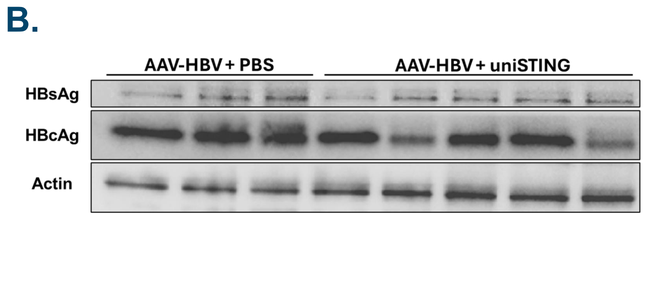




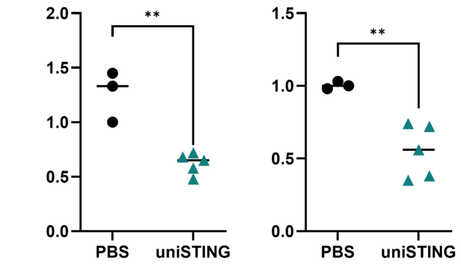
- Mice inoculated with AAV-HBV were administered with two doses of uniSTING.
- Mice were bled every four weeks and euthanized at 13wpi.
- HBV DNA was extracted from plasma and measured by qPCR.
- Serum HBsAg and anti-HBs IgG were measured by ELISA.

6. uniSTING treatment stably suppresses intrahepatic HBV replication.





- At 13wpi, mice were euthanized. RNAs and proteins were extracted from snap-frozen liver tissues.
- HBV RNA was measured by RT-qPCR.
- HBV proteins were measured by immunoblot.



Conclusions

1. In vitro uniSTING stimulation led to strong reduction in HBV cccDNA gene expression.
2. Administration of uniSTING in naïve mice triggered robust IFN-β and ISG responses, but not in HBV carrier mice.
3. Repeated treatment of uniSTING in HBV carrier mice resulted in stable reductions of serum HBV DNA and HBsAg.
4. uniSTING elicited anti-HBs IgG responses, demonstrating the ability to break immune tolerance.

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