Preclinical study of a combinatorial RNAi/vaccination therapy as a potential functional cure for chronic hepatitis B

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BACKGROUND and AIM

Hepatitis B cure is highly desired, but rarely achieved with current therapies. Hepatitis B Virus (HBV) persistence was found to correlate with a failure to develop an efficient virus-specific T cell response due to high HBV antigen load (Ref. 1). RNAi is a promising approach to control HBV replication and lower antigen load. We evaluated the capacity of stabilized, liver-targeted siRNAs to (i) suppress HBV gene expression, (ii) allow recovery of HBV-specific B- and T-cell responses.

METHODS

The HBV genome is highly condensed and all transcripts have an identical 3’ end which allows simultaneous suppression of all HBV transcripts and proteins with one siRNA/shRNA (A). Conjugation of siRNAs to N-Acetylgalactosamine (GalNAc) allows hepatocyte-specific delivery (B).

RESULTS

Effect of pretreatment on HBV parameters

Monthly subcutaneous injections of 3 mg/kg GalNAc-shRNAs as well as i.v. injected 1x1011 particles AAV-shHBV efficiently suppressed viral transcripts in liver (A) and HBV antigens and DNA in serum (B). HBsAg and HBV DNA were reduced by 2 log10 and HBcAg by 1 log10. ETV strongly reduced HBV DNA by 4 log10, but antigen levels remained unchanged. siRNA and subsequent therapeutic vaccination showed an additive effect on HBsAg and HBV-DNA levels cumulating in >4 log10 reductions compared to pretreatment levels.

DURATION OF ANTIGEN SUPPRESSION

Experimental setup

We now compared different durations of antigen suppression to determine the optimal time point of vaccination. siRNA therapy was started 3, 6, or 8 weeks prior to start of therapeutic vaccination (A).

Effect on T cell responses

The duration of siRNA pretreatment positively correlated with the intrahepatic HBV-specific CD8 T cell responses after therapeutic vaccination (B).

Effect on HBV parameters

Conform with stronger HBV-specific CD8 T cell responses, there was an increased suppression of HBsAg with longer siRNA-pretreatment before vaccination. The best treatment scheme resulted in a >5 log10 reduction of HBsAg to undetectable levels in all treated animals.

Effect of pretreatment on B cell responses

The heterologous prime-boost vaccination of induced B-cell immunity and anti-HBs-seroconversion in all animals but there was no effect of HBV antigen suppression on B cell responses. No anti-HB antibodies could be detected (not shown).

CONCLUSIONS

We developed a combinatorial RNAi/vaccination therapy for hepatitis B that, after finite treatment, allows reconstitution of HBV-specific T cell responses and suppression of HBsAg to undetectable levels in a preclinical mouse model of chronic hepatitis B, suggesting substantial potential for clinical translation.

REFERENCES

1. Michler&Kosinska et al. EASL 2016 (Abstract#LC2016-RS-1449)

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