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Pegylated Interferon Lambda efficiently suppresses HDV productivity and shows comparable ability to induce ISGs as peg-IFNα in HBV/HDV co-infected humanized mice

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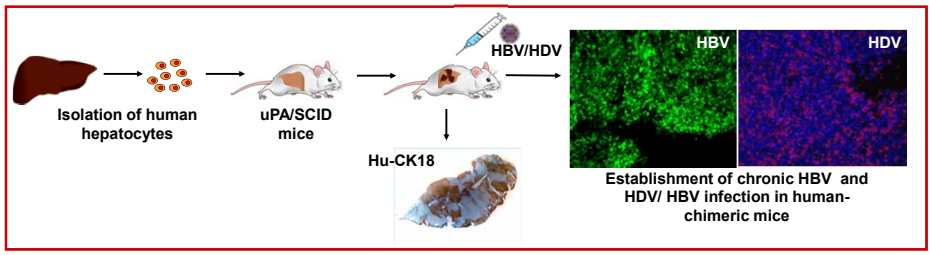
Background: The interferon system plays a fundamental role in counteracting viral infections. Like interferon-alpha (IFNα), interferon-lambda (IFNλ) induces antiviral activity in hepatocytes. Because its receptor is largely restricted to cells of epithelial origin, IFNλ may induce an antiviral state via the activation of interferon stimulated genes (ISGs), while showing fewer side effects. Although IFNλ was reported to suppress HBV replication in vitro and in HBV-transgenic mice, the impact of IFNλ on hepatitis Delta virus (HDV) infection has not been investigated.



Aim of the study was to determine the antiviral effect of peg-IFNλ on HDV productivity and to explore its ability to induce the innate immune system of the human hepatocytes compared to peg-IFNα in human liver-chimeric uPA/SCID mice.

Methods: Chronic HBV/HDV co-infected mice were treated either with peg-IFNα or peg-IFNλ for 4 weeks (**Figure 1A**). Viremia and ISG levels were determined by qRT-PCR, intrahepatic genomic and antigenomic HDV-RNA by using a novel qRT-PCR assay and HDAg by immunohistochemistry.

Peg-IFNλ provoked the reduction of HDV and HBV viremia and circulating HBsAg

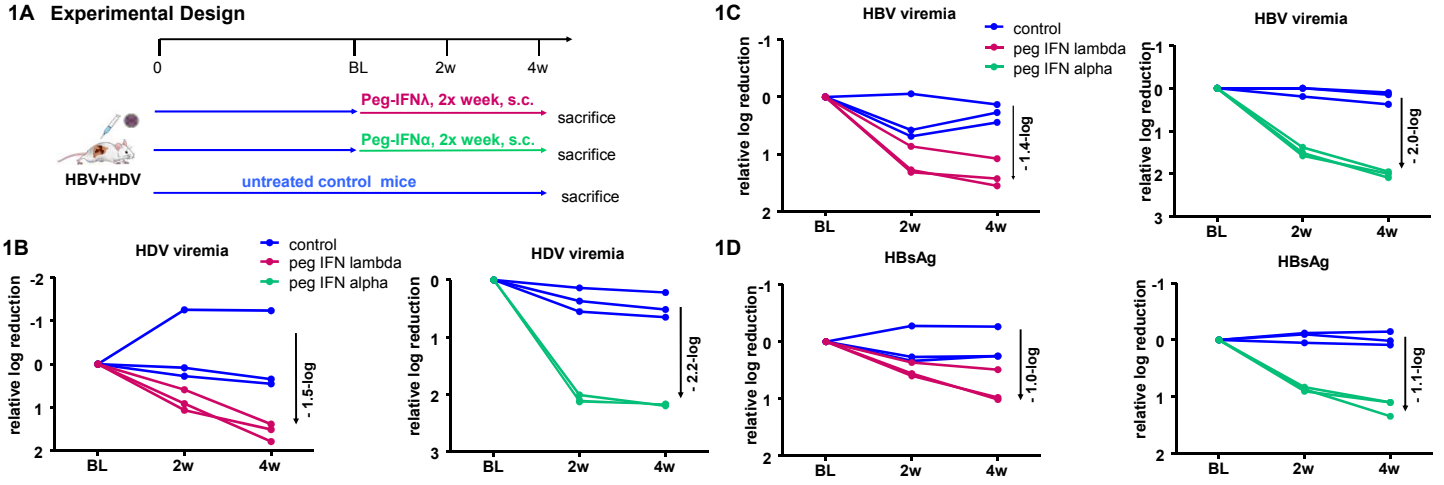


Figure 1. 4 weeks of peg-IFNλ administration decreased median HDV viremia by 1.5-log (**B**), HBV viremia by 1.4-log (**C**) and circulating HBsAg by 1.0-log (**D**), although its antiviral effects were not superior to those of IFNα (HDV 2.2log-; HBV 2.0log-; HBsAg 1.1log-reduction; **B-D**).

Peg-IFNλ suppresses intrahepatic levels of HDV and HDAg

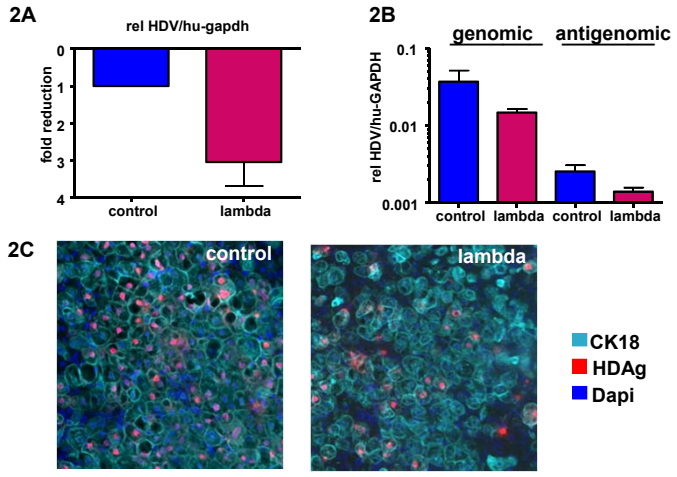


Figure 2. Compared to untreated control mice, IFNλ treated animals showed a 2.6- and 1.9-fold decrease of intrahepatic genomic and antigenomic HDV-RNA/human GAPDH, respectively, as well as lower amounts of HDAg-positive human hepatocytes.

IFN-mediated enhancement of ISGs & cytokines expression

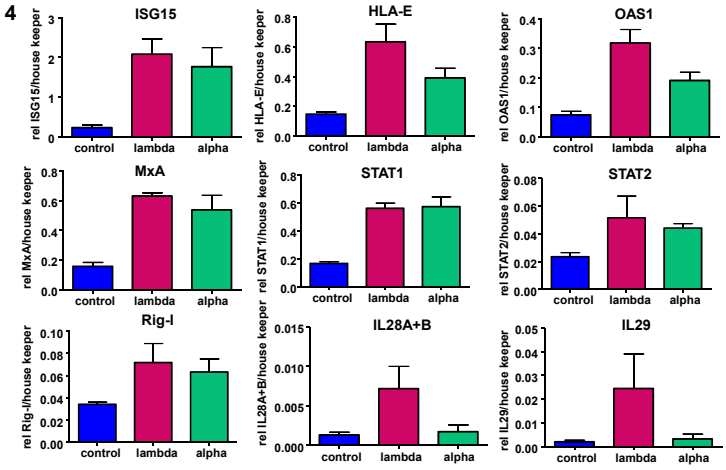


Figure 4. IFNλ provoked a clear induction of human ISGs (i.e. ISG15=6.2-fold, HLA-E=4.2-fold, MxA=3.9-fold) and signalling genes, as Rig-I (1.9-fold), STAT1 (3.4-fold) and STAT2 (2.1-fold) in HBV/HDV co-infected mice, which was comparable to IFNα. Notably, IFNλ but not IFNα administration enhanced the expression of endogenous human IFN-lambda genes (IL28A+B=4.3-fold; IL29=11.2-fold).

Conclusions:

Similarly to IFNα, IFNλ efficiently suppressed HDV productivity (viremia, intrahepatic HDV-RNA levels and amounts of HDAg-positive cells) and strongly enhanced the innate immune responses of the human hepatocytes. However, the self-induction of IFNλ genes was unique and underlay the diverse capacities of these IFNs to trigger distinct antiviral pathways, which may prove useful for the development of more effective therapeutic concepts.