In vivo model for HBV-HIV coinfection studies

#0219

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ABSTRACT

Background: The interplay between innate immune responses of hepatocytes to HBV in the setting of ongoing HIV-1 replication requires in vivo model system. The underlying mechanisms by which HBV-induced liver pathogenesis is affected by HIV co-infection remain unknown due in large part to the lack of small animal models. Such model is crucial for the development of novel therapies, treating HBV/HIV-coinfections and associated liver diseases.

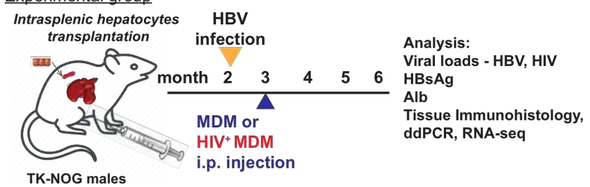
There are several unresolved problems in mice co-transplanted with human hepatocytes and immune cells: transplantation of mismatched by HLA genotypes hepatocytes and hematopoietic stem cells contains a risk for allograft rejection and the low functionality of adaptive immune responses.

We hypothesize that human hepatocyte transplanted mice, infected with HBV and co-transplanted with human HIV-1-infected or uninfected macrophages will reproduce the features of viral interaction.

Methods: TK-NOG mice were transplanted with human hepatocytes, and after confirmation of the human albumin concentration in peripheral blood, animals were infected with HBV 10^7 GE/mouse (subtype D ayw). Following confirmation of HBV DNA presence in peripheral blood (~$1.5x10^4$ copies/ml), animals were injected with human monocyte-derived macrophages (MDM) or HIV-exposed MDM ($5x10^6$ cells/mouse i.p.) and controls kept without MDM. Animals were observed for 51 days and levels of HIV RNA, HBV DNA, HBsAg in plasma were monitored. At end-point liver tissues were analyzed for histopathology, presence of viruses and human MDM by RT-PCR, and staining for human cells and viral proteins.

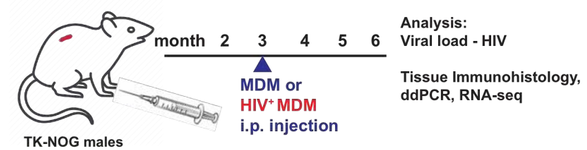
Material and Method

Experimental group



Analysis:
Viral loads - HBV, HIV
HBsAg
Alb
Tissue Immunohistology, ddPCR, RNA-seq

Control MDM only group



Analysis:
Viral load - HIV

Tissue Immunohistology, ddPCR, RNA-seq

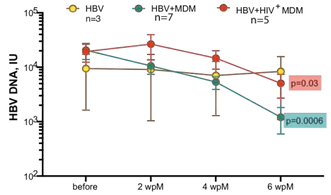
Conclusion: This study utilizes a novel humanized mouse model that fill the critical knowledge gaps on the mechanism by which HBV/HIV co-infection accelerates liver diseases and is the first model to observe changes in HBV and HIV-1 replication pattern and tissue histopathology and transcriptomics.

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RESULTS

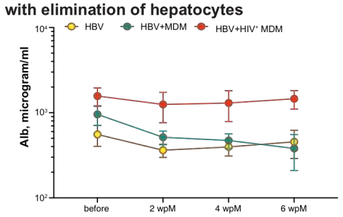
A. Peripheral blood of HBV-HIV coinfected mice

1. Macrophages reduced HBV replication and HIV-1 infection weakened their protective effects

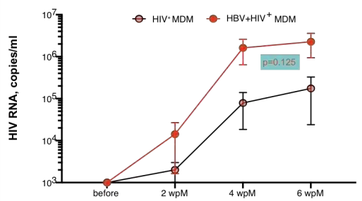


P values show differences of parameters between before injection of macrophages and the end-point of observation.

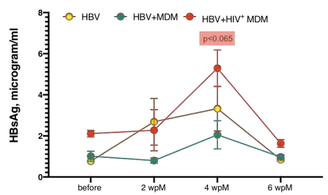
2. Reduced HBV replication was not associated with elimination of hepatocytes



3. HBV replication trends to augment HIV-1 replication



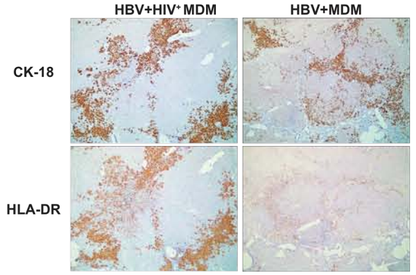
4. HIV replication augments HBsAg concentration



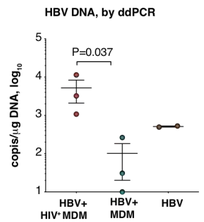
P values show differences of parameters between animals injected with uninfected and HIV-1 infected macrophages.

B. Livers of HBV-HIV coinfected mice

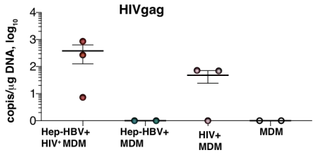
1. Coinfection increased MHC II antigen expression on hepatocytes



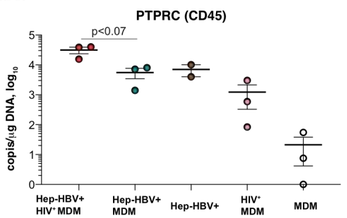
2. Coinfected animals retained HBV DNA compared to uninfected macrophages transplanted



3. Coinfected animals retained HIV DNA

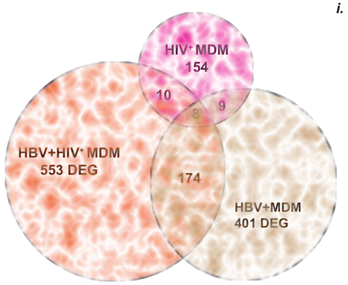


4. Human hepatocyte transplanted animals have human immune cells and HBV-HIV-1 coinfection trends to increase their number



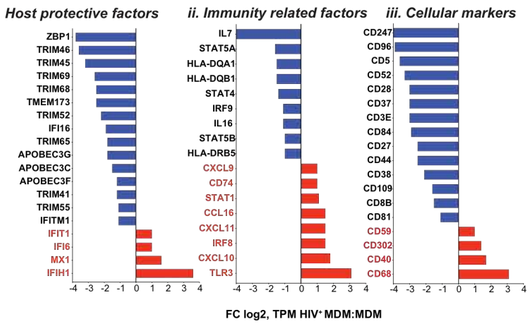
C. Findings in livers of HBV-HIV coinfected mice by RNA-seq

1. Numbers of differentially expressed genes (DEG)



versus HBV infected
n=2 per group

2. Differences in effects of uninfected and HIV-1 infected MDM



3. GeneAnalytics - Pathway results. High score match

