Research Project Proposal
Academic year 2020-2021

Máster en Investigación Biomédica

Project Nº 16

Title: Development of new therapeutic alternatives against HDV infection based on RNA editing strategies

Department/ Laboratory *Laboratory of gene therapy for hepatic diseases. Dept. of Gene Therapy and Regulation of gene expression. CIMA.*

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Summary

According to the WHO around 20 million individuals are chronically infected with the hepatitis delta virus (HDV) worldwide and more recent reports suggested that the number of HDV positive individuals may even be even higher (1). HDV is a defective RNA virus that requires the surface antigens of hepatitis B virus (HBV) (HBsAg) for viral assembly and transmission.

The HDV genome is a circular, negative, single-stranded genomic RNA, which folds into an unbranched rod-like structure with many paired nucleotides. HDV redirects the host RNA polymerase II to amplify the viral genome via a double rolling circle amplification process, which leads to the accumulation of two other RNAs in infected hepatocytes (4,5). The antigenomic RNA is an exact complement of the genome and the smaller linear mRNA encodes for the only known viral protein, the hepatitis delta antigen (HDAg), which exists in two different forms. The small HDAg is important for virus replication, whereas the large variant inhibits replication and promotes virion assembly. Production of the L-HDAg by post-transcriptional RNA editing at adenosine 1012 (amber/W site) is mediated by a RNA-specific adenosine deaminase (ADAR) and represents a valid HDV replication marker (5).

We have developed a unique mouse model based on the transfer of HDV and HBV replication competent genomes using recombinant adenoassociated virus (AAV) as vehicles. This mouse model recapitulates most of the characteristics of HDV human infection and is a highly valuable tool to better understand the interaction of the virus with the host cells and to develop new therapies (5).

The goal of this project is to develop new therapeutic strategies against HDV infection using CRISPR-based system for recognizing and degrading the intracellular viral genome and its resulting viral mRNAs. More specifically Cas13 RNA editing enzyme and HDV-specific guide sequences will be used to destroy viral RNA and control viral infection, an strategy that has been recently demonstrate to work with RNA viruses (8,9).

yes	**X**
no	

Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator?