Biochemical and Biophysical Research Communications 466 (2015) 567–571

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

The sirtuin inhibitor sirtinol inhibits hepatitis A virus (HAV) replication by inhibiting HAV internal ribosomal entry site activity

Tatsuo Kanda [a, *], Reina Sasaki [a], Shingo Nakamoto [a, b], Yuki Haga [a], Masato Nakamura [a], Hiroshi Shirasawa [b], Hiroaki Okamoto [c], Osamu Yokosuka [a]

[a] Department of Gastroenterology and Nephrology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan
[b] Department of Molecular Virology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan
[c] Division of Virology, Department of Infection and Immunity, Jichi Medical University School of Medicine, Shimotsuke, Japan

ARTICLE INFO

Article history:
Received 24 August 2015
Accepted 14 September 2015
Available online 24 September 2015

Keywords:
HAV
IRES
JNJ-7706621
Sirtinol

ABSTRACT

Epigenetics plays a role in the regulation of gene expression. Epigenetic changes control gene expression at the transcriptional level. Our previous study suggested that the La protein, which is mainly localized in the nucleus, was associated with hepatitis A virus (HAV) internal ribosomal entry site (IRES)-mediated translation and HAV replication. The aim of this study was to investigate whether epigenetic compounds have effects on HAV IRES-mediated translation and HAV replication. Sirtinol, a sirtuin inhibitor, inhibited HAV IRES-mediated translation in COS7-HAV-IRES cells. Treatment with 10 μM sirtinol resulted in a significant reduction in the intracellular RNA levels of HAV HA11-1299 genotype IIIA in Huh7 cells. Epigenetic treatment with a sirtuin inhibitor may represent a new treatment option for HAV infection. In conclusion, epigenetic control was involved in HAV IRES-dependent translation and HAV replication. Special attention should also be paid to underlying viral diseases in the clinical use of epigenetic treatments for malignancies.

© 2015 Elsevier Inc. All rights reserved.

1. Introduction

Hepatitis A virus (HAV) infection is a major cause of acute hepatitis and liver failure in both developing and developed countries [1–5]. In spite of the development of effective vaccines against HAV, in recent years, patients hospitalized for hepatitis A in the United States have been older and more likely to have liver diseases and other comorbid medical conditions, such as hypertension, ischemic heart disease, disorders of lipid metabolism, and chronic kidney disease [6]. The development of drugs against HAV may improve these conditions.

HAV is a single-stranded, positive-sense RNA virus that is 7.5 kb in length that belongs to the *Picornaviridae* family. The HAV genome is flanked by a 5′ non-translated region (NTR) and a 3′ NTR, and it encodes structural (VP4, VP2, VP3 and VP1) and non-structural proteins (2A, 2B, 2C, 3A, 3B, 3C and 3D) [7]. It also possesses an internal ribosomal entry site (IRES) that is a responsible for cap-independent translation initiation. The nucleotide sequence of the HAV IRES is conserved among different HAV genotypes and is consequently a candidate antiviral target [7–9].

Recently, we reported that the Janus kinase (JAK) inhibitors SD1029, AG490 and AZD1480 reduced host factor La protein expression and inhibited HAV IRES activity and HAV replication [10,11]. Thus, human La protein, which is predominantly localized in the nucleus and is associated with RNA metabolism [12], is involved in HAV IRES-dependent translation and replication [10,11], although HAV seems to replicate in the cytoplasm of hepatocytes.

Epigenetic compounds such as histone deacetylase (HDAC) inhibitors have effects on the transcription of many genes and have also been shown to have anti-cancer [13] and/or anti-viral properties [14]. In the present study, we investigated the effects of epigenetic compounds on HAV IRES-dependent translation and HAV replication.

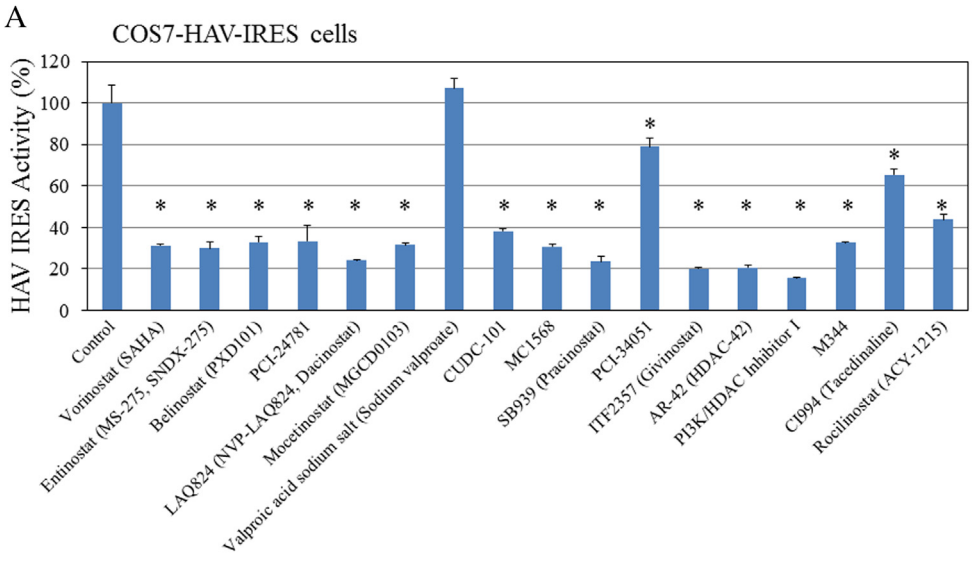
2. Materials and methods

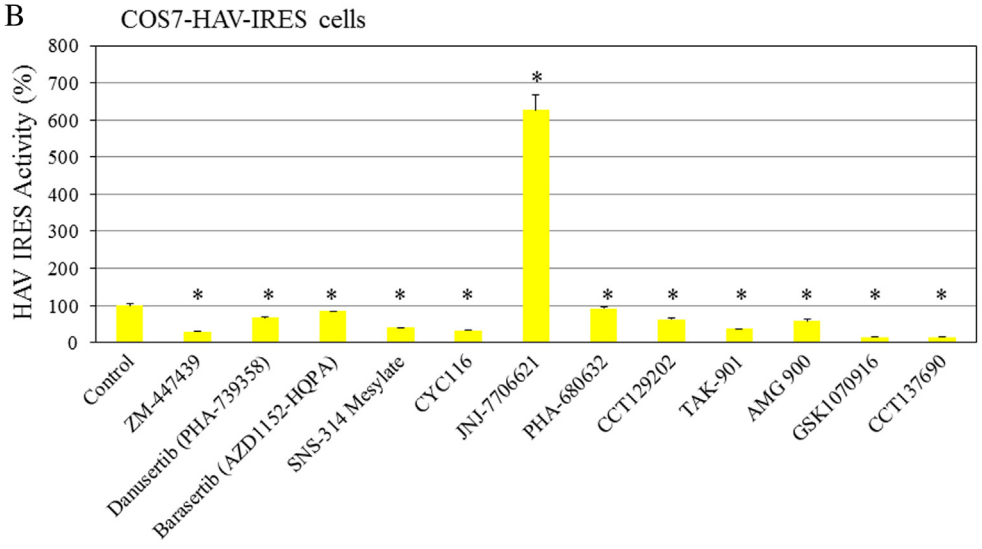
2.1. Cell lines and reagents

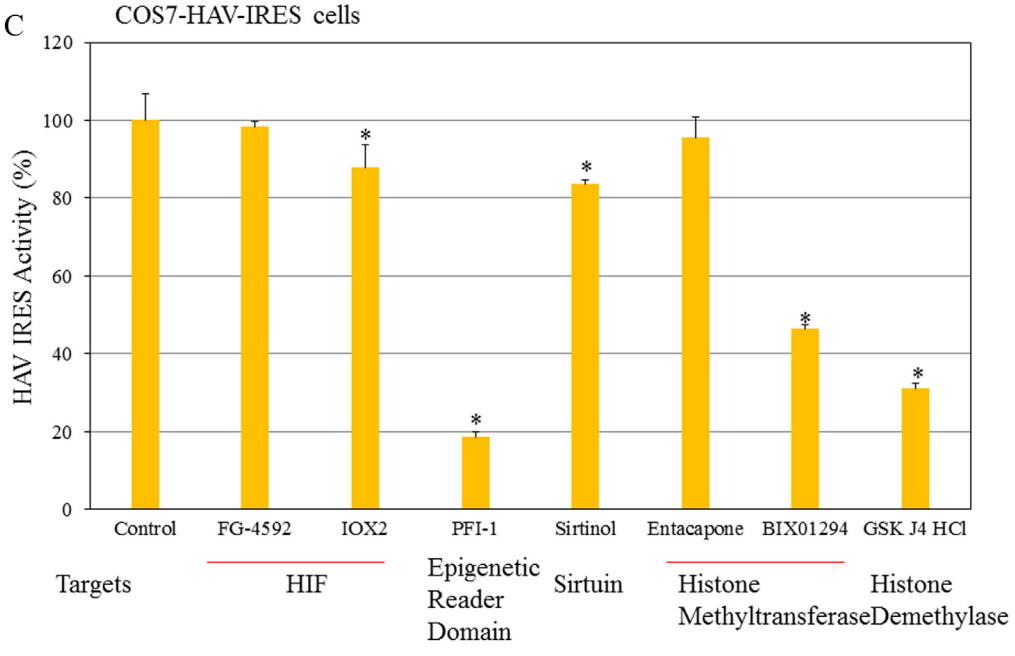
The human hepatoma cell line Huh7 and the African green monkey kidney cell line COS7 were maintained in Dulbecco's

* Corresponding author.
E-mail address: kandat-cib@umin.ac.jp (T. Kanda).

http://dx.doi.org/10.1016/j.bbrc.2015.09.083
0006-291X/© 2015 Elsevier Inc. All rights reserved.


A
COS7-HAV-IRES cells
HAV IRES Activity (%)
120
100
80
60
40
20
0
Control
Vorinostat (SAHA)
Entinostat (MS-275, SNDX-275)
Belinostat (PXD101)
PCI-24781
LAQ824 (NVP-LAQ824, Dacinostat)
Mocetinostat (MGCD0103)
Valproic acid sodium salt (Sodium valproate)
CUDC-101
MC1568
SB939 (Pracinostat)
PCI-34051
ITF2357 (Givinostat)
AR-42 (HDAC-42)
PI3K/HDAC Inhibitor I
M344
CI994 (Tacedinaline)
Rocilinostat (ACY-1215)


B
COS7-HAV-IRES cells
HAV IRES Activity (%)
800
700
600
500
400
300
200
100
0
Control
ZM-447439
Danusertib (PHA-739358)
Barasertib (AZD1152-HQPA)
SNS-314 Mesylate
CYC116
JNJ-7706621
PHA-680632
CCT129202
TAK-901
AMG 900
GSK1070916
CCT137690


C
COS7-HAV-IRES cells
HAV IRES Activity (%)
120
100
80
60
40
20
0
Control
FG-4592
IOX2
PFI-1
Sirtinol
Entacapone
BIX01294
GSK J4 HCl
Targets
HIF
Epigenetic Reader Domain
Sirtuin
Histone Methyltransferase
Histone Demethylase

Download English Version:

https://daneshyari.com/en/article/10750950

Download Persian Version:

https://daneshyari.com/article/10750950

Daneshyari.com