ISSN 2644-3236 (online)

Artificial Intelligence in *Gastroenterology*

Artif Intell Gastroenterol 2021 February 28; 2(1): 1-9

Published by Baishideng Publishing Group Inc

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Artificial Intelligence in Gastroenterology

Contents

Bimonthly Volume 2 Number 1 February 28, 2021

MINIREVIEWS

1 Artificial intelligence and machine learning could support drug development for hepatitis A virus internal ribosomal entry sites

Kanda T, Sasaki R, Masuzaki R, Moriyama M

Artificial Intelligence in Gastroenterology

Bimonthly Volume 2 Number 1 February 28, 2021

Contents

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AIG mainly publishes articles reporting research results obtained in the field of artificial intelligence in gastroenterology and covering a wide range of topics, including artificial intelligence in gastrointestinal cancer, liver cancer, pancreatic cancer, hepatitis B, hepatitis C, nonalcoholic fatty liver disease, inflammatory bowel disease, irritable bowel syndrome, and *Helicobacter pylori* infection.

INDEXING/ABSTRACTING

There is currently no indexing.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Jia-Hui Li*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Jin-Lei Wang*.

NAME OF JOURNAL
Artificial Intelligence in Gastroenterology

ISSN
ISSN 2644-3236 (online)

LAUNCH DATE
July 28, 2020

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Rajvinder Singh, Ferruccio Bonino

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2644-3236/editorialboard.htm

PUBLICATION DATE
February 28, 2021

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Artificial Intelligence in Gastroenterology

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Artif Intell Gastroenterol 2021 February 28; 2(1): 1-9

DOI: 10.35712/aig.v2.i1.1

ISSN 2644-3236 (online)

MINIREVIEWS

Artificial intelligence and machine learning could support drug development for hepatitis A virus internal ribosomal entry sites

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Author contributions: Kanda T performed the majority of the writing and prepared the figures and tables; Sasaki R performed data acquisition and writing; Masuzaki R provided input in writing the paper; Moriyama M designed the outline and coordinated the writing of the paper; all authors have read and approve the final manuscript.

Supported by The Japan Agency for Medical Research and Development, No. JP20fk0210075.

Conflict-of-interest statement: There is no conflict of interest associated with any authors who contributed their efforts to this manuscript.

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Abstract

Hepatitis A virus (HAV) infection is still an important health issue worldwide. Although several effective HAV vaccines are available, it is difficult to perform universal vaccination in certain countries. Therefore, it may be better to develop antivirals against HAV for the prevention of severe hepatitis A. We found that several drugs potentially inhibit HAV internal ribosomal entry site-dependent translation and HAV replication. Artificial intelligence and machine learning could also support screening of anti-HAV drugs, using drug repositioning and drug rescue approaches.

Key Words: Artificial intelligence; Hepatitis A virus internal ribosomal entry sites; Cap-independent translation; Antivirals; Severe hepatitis A; Glucose-regulated protein 78

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Core Tip: In certain areas, it is difficult to perform universal hepatitis A virus (HAV) vaccination. We found that several drugs potentially inhibit HAV internal ribosomal entry sites-dependent translation and HAV replication. After the application of machine and deep learning, artificial intelligence identified effective anti-HAV drugs more quickly, using drug repositioning and drug rescue.

Citation: Kanda T, Sasaki R, Masuzaki R, Moriyama M. Artificial intelligence and machine learning could support drug development for hepatitis A virus internal ribosomal entry sites. *Artif Intell Gastroenterol* 2021; 2(1): 1-9

URL: https://www.wjgnet.com/2644-3236/full/v2/i1/1.htm

DOI: https://dx.doi.org/10.35712/aig.v2.i1.1

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Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Japan

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): E

Received: October 15, 2020
Peer-review started: October 15, 2020
First decision: December 17, 2020
Revised: December 29, 2020
Accepted: February 12, 2021
Article in press: February 12, 2021
Published online: February 28, 2021

P-Reviewer: Raiter A, Ravaioli F
S-Editor: Wang JL
L-Editor: A
P-Editor: Li JH

INTRODUCTION

Infection with hepatitis A virus (HAV) can lead to acute hepatitis, occasionally resulting in acute liver failure, which is associated with death or liver transplant-ation[1,2]. In developing countries, HAV generally infects humans in childhood, and people have immunity against HAV without HAV vaccination[3]. In India, however, the prevalence of anti-HAV antibodies is lower now in adolescents and young adults (approximately 55% in 5-15 years in India) than before (approximately 90%)[3]. In some developed countries where there are no universal vaccination programs, such as Japan, people have less immunity against HAV than levels observed in the past[4,5].

HAV infects humans through the fecal-oral route when HAV-contaminated foods and water are ingested[6]. Recently, hepatitis A has also been recognized as a sex-transmitted disease[7]. Several effective HAV vaccines are available, but they are relatively expensive, and in some countries, it is difficult to perform universal vaccination[4,5]. Therefore, to prevent severe hepatitis A, it may be better to develop antivirals against HAV[8].

Recently, information and communication technology, and artificial intelligence (AI) have played roles in daily clinical practice[9,10]. AI also plays an important role in drug discovery[11]. With the progress of machine learning methods and the accumulation of pharmacological data, AI has become a powerful data mining tool in the area of drug discovery, such as *in silico* screening, quantitative structure-activity relationship (QSAR) analysis, *de novo* drug design, and *in silico* evaluation of absorption, distribution, metabolism, excretion and toxicity[12].

Structure-based drug design is becoming an essential tool for faster, more cost-efficient drug discovery, compared to traditional methods[13]. The combination of AI and deep learning, which is a family of machine learning models that use artificial neural networks, may be a more powerful tool for drug discovery. The associations of machine learning, deep learning and AI are shown in Figure 1. Moreover, network-based *in silico* drug efficacy screening allows us to predict novel drug-disease associations, which may provide us with drug repositioning or drug rescue information[14]. In this minireview article, we discuss the recent involvement of AI in drug discovery and its application in the development of antivirals against HAV in the near future.

HAV INTERNAL RIBOSOMAL ENTRY SITE-DEPENDENT TRANSLATION AND HAV REPLICATION

Translation of HAV protein is performed in a cap-independent manner under the control of the internal ribosomal entry site (IRES), which is mainly located at 5' untranslated region (5'UTR)[15]. It was reported that the HAV 5'UTR was more than 25-fold less active than the encephalomyocarditis virus IRES in producing translated proteins[16]. Thus, the relatively weaker activity of the HAV IRES may be due to a reduced affinity for several cellular translation factors[16]. Mutations within the HAV 5'UTR could enhance cap-independent translation in African green monkey kidney BS-C-1 cells[17]. Further studies are needed to identify specific mutations related to the severity of hepatitis A[18-20], although among HAV strains from HAV outbreaks in Korea and Japan, we did not identify specific mutations associated with severe hepatitis A in the HAV 5'UTR[21,22]. We also demonstrated that the inhibition of HAV IRES activity by small interfering RNAs (siRNAs) targeting HAV IRES could lead to the suppression of HAV replication[23]. Therefore, HAV IRES is an attractive target of antivirals against HAV.

IMPORTANT FACTORS INTERACTING WITH HAV IRES

HAV is a nonenveloped and enveloped positive-sense single-stranded RNA virus approximately 7.6 kb in length[24,25]. The HAV genome includes a 5'UTR, one open reading frame encoding structural (VP4, VP2, VP3, VP1 and 2A) and nonstructural proteins (2B, 2C, 3A, 3B, 3C and 3D) and a 3'UTR[26].

Among HAV proteins, HAV proteinase 3C suppressed HAV IRES-dependent translation[27]. Furthermore, HAV 3C cleaves the polypyrimidine tract-binding protein (PTB), which interacts with the HAV IRES[27,28]. Among host proteins, autoantigen La[27], glyceraldehyde-3-phosphate dehydrogenase[29], PTB[28], poly(C) binding protein 2[30], polyadenylate-binding protein-1[31], eukaryotic translation

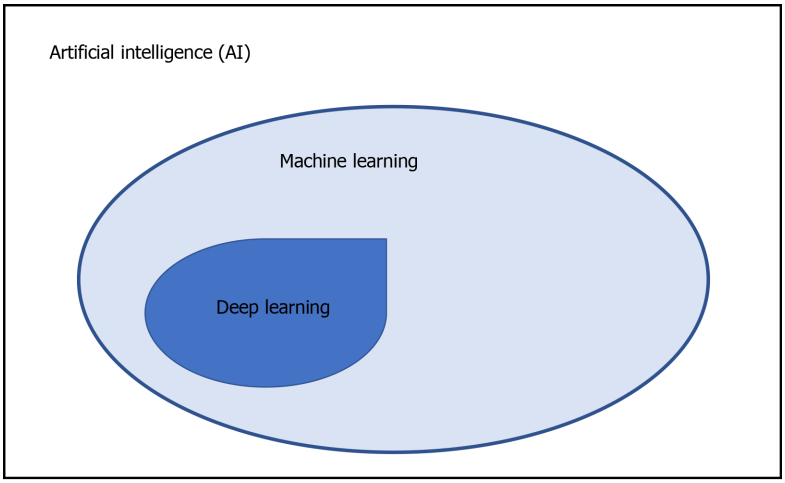

Figure 1 Association of artificial intelligence, machine learning and deep learning.

initiation factor 4E[32] and eukaryotic translation initiation factor 4E[33] are reported to interact with HAV IRES.

We demonstrated that siRNA against cellular cofactors for HAV IRES could inhibit HAV IRES-mediated translation[34]. The Janus kinase (JAK) inhibitors SD-1029 and AG490 could reduce La protein expression and inhibit HAV IRES-mediated translation as well as HAV replication[34]. The JAK2 inhibitor AZD1480 could reduce La expression and inhibit HAV IRES activity and HAV replication[35]. We also reported that the sirtuin inhibitor sirtinol[36] and broad-spectrum antivirals, such as amantadine[20,37,38], interferon-alpha[38] and interferon-lambda (interleukin-29)[39], could inhibit HAV IRES-mediated translation and HAV replication. Thus, *in vitro* drug screening with human hepatocytes revealed that several drugs inhibit HAV replication through the inhibition of HAV IRES activity.

BIOINFORMATICS AND CHEMINFORMATICS

Bioinformatics and cheminformatics are newer strategies to screen and design various drug candidates for HAV, as performed for severe acute respiratory syndrome coronavirus 2 in the coronavirus disease 2019-era[40]. Das *et al*[41] performed a genome-wide CRISPR screen and identified 39 candidate essential hepatovirus host factors, which form 4 clusters as follows: HAV IRES-mediated translation, chaperone activity, mitochondrial integrity and ganglioside synthesis. This strategy seems to result in the generation of more accurate approaches and techniques for HAV management.

STRUCTURE-BASED DRUG DESIGN

Crystallization of HAV IRES and formation of its drug modification

HAV needs a HAV 3C protease to form its viral replication complex. X-ray structures were reported for HAV 3C protease with HAV 3C protease inhibitor *N*-benzyloxy-carbonyl-l-serine-β-lactone (1a), resulting in a lead compound that was further developed to produce a potent inhibitor of HAV 3C protease through the alkylation of the sulfur atom at the active site Cys172[42]. Furthermore, soaking *N*-iodoacetyl-valine-phenylalanine-amide, which inhibited HAV 3C protease activity, into HAV 3C–1a crystals through the modification of His102 $N^{\varepsilon 2}$-alkylated protein could lead to the successful utilization of this new crystal form in the study of enzyme–inhibitor interactions in the proteolytic active site[42]. In general, antivirals are used after hepatitis virus infects the liver. It may be better to prevent infection rather than to treat HAV.

Koirala *et al*[43] also reported a 2.84-Å resolution crystal structure of HAV IRES domain V in complex with a synthetic antibody fragment - a crystallization chaperone. This is useful for drug repositioning to compare other picornaviral HAV structures with those of HAV.

AI, MACHINE LEARNING AND DEEP LEARNING

AI and machine learning can contribute to drug development for viral infection by improving the speed and efficiency of repurposing and proposing new potent molecules to inhibit viral replication[40]. Both AI and machine learning can also be employed to make network-based predictions of drug-target interactions[44] or associations between gene expression and HAV infection[45]. This information is crucial to feed into AI and machine learning systems for the development of potent anti-HAV drugs. Although new drug discovery typically takes more than 10 years[46], this method may be useful for drug repositioning and drug rescue, which allows us to develop anti-HAV drugs more quickly. For example, the hepatitis C virus (HCV) NS5B polymerase inhibitor sofosbuvir and its derivatives could suppress HAV replication[47,48].

Many human proteins are involved in viral replication and pathogenesis[8,48]. The advantage of host-targeted antivirals is that the target is abundant. Another advantage is that they are less prone to resistance than those directly targeting the virus[8,49]. We and others also reported that host-targeted antivirals are useful for the suppression of HAV replication[8,34,35,50-53]. We would like to apply AI, machine learning and deep learning methods for drug repositioning and rescue to discover anti-HAV drug candidates (Figure 2). AI, machine learning and deep learning methods may also be useful for the avoidance of drug side effects.

MACHINE LEARNING AND DRUG DEVELOPMENT FOR HEPATITIS VIRUSES AND GLUCOSE-REGULATED PROTEIN 78

Hepatitis B virus

Qureshi *et al*[54] developed virus-specific as well as general QSAR models and computed approximately 18000 chemical descriptors (1D, 2D and 3D), including geometric, constitutional, electrostatic, topological, hydrophobic and binary fingerprints, using PaDEL, an open-source software to calculate molecular descriptors and fingerprints[54]. They also employed SVMlight software (Freely available at http://svmlight.joachims.org) for machine learning. After attribute selection, there were 15 relevant descriptors for HBV. Arora *et al*[55] performed a QSAR study based on a series of anti-hepatitis B virus (HBV) agents, namely, a series of novel bis(Lamino acid) ester prodrugs of 9-[2-(phosphonomethoxy)ethyl]adenine, a similar series of compounds comprising 2-amino-6-arylthio-9-[2-(phosphonoethoxy)ethyl] purine bis(2,2,2-trifluoroethyl) esters, and a series of 1-isopropylsulfonyl-2-amine benzimidazoles. These systems may also be useful for the development of anti-HAV drugs.

Deep learning has been applied for the diagnosis and treatment of chronic hepatitis B. Compared with two-dimensional shared wave elastography and fibrosis biomarkers, deep learning radiomics of elastography is valuable and practical as a noninvasive accurate diagnosis of liver fibrosis in HBV-infected patients[56]. Analysis of the quasispecies pattern of HBV genomes by the combination of deep sequencing and machine learning is also useful for the prediction of hepatocellular carcinoma (HCC) and direct therapeutic strategies[57,58]. A valid systematic approach based on big data mining and genome-wide RNA-seq data may be imperative to further investigate the pathogenic mechanism and identify biomarkers for drug design[59].

HCV

Weidlich *et al*[60] developed SAR with advanced machine learning methods and performed *in vitro* antiviral assays, resulting in the identification of the candesartan cilexetil, which is used to treat hypertension, as an HCV NS5B inhibitor. Using a support vector machine (SVM), three classification models were built in HCV NS3 protease inhibitors[61] or HCV NS5B polymerase inhibitors[62]. Qin *et al*[63] reported that the combination of the best sub- and whole dataset SVM models can be used as reliable lead design tools for new NS3/4A protease inhibitors.

Wei *et al*[64] reported that the multiple QSAR method is useful in predicting chemical-protein interactions for the discovery of multitarget inhibitors for the treatment of HIV/HCV coinfection. This strategy may be useful for the treatment of the cooccurrence of HAV infection and chronic liver disease[65].

Combination information from yeast-based library screening, next-generation sequencing, and structure-based modeling in a supervised machine learning approach is useful for the comprehensive sequence-energetics-function mapping of the

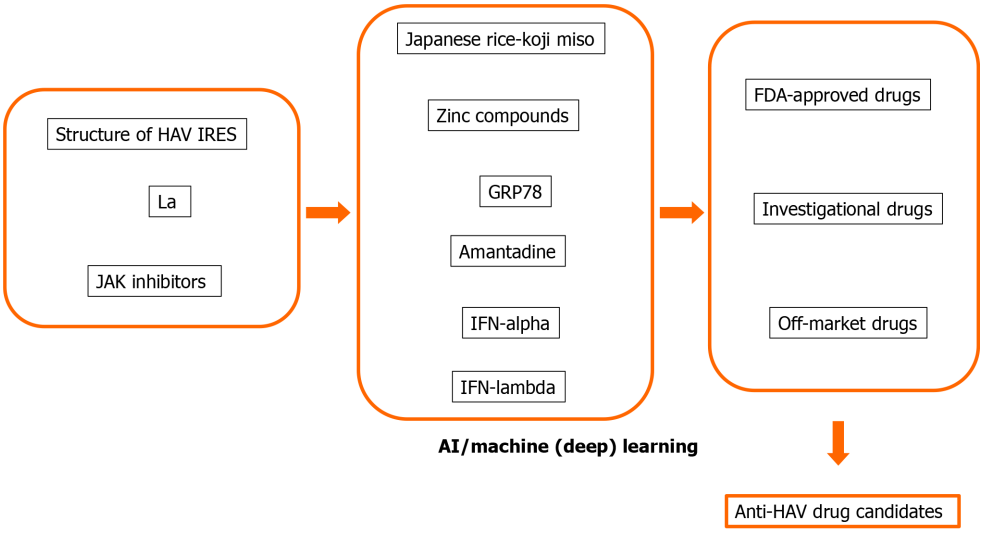

Figure 2 Drug screening and drug discovery for anti-hepatitis A virus using artificial intelligence-based drug repositioning and rescue.
HAV: Hepatitis A virus; AI: Artificial intelligence; IRES: Internal ribosomal entry-site; La: Lupus La protein/SSB; JAK: Janus kinase; GRP: Glucose-regulated protein; IFN: Interferon; FDA: Food and Drug Administration.

specificity landscape of the HCV NS3/4A protease, whose function-site-specific cleavages of the viral polyprotein are a key determinant of viral fitness[66]. Deep learning recurrent neural network models could be used to identify patients with HCV-related cirrhosis with a high risk of developing HCC for risk-based HCC outreach and surveillance strategies[67]. Deep learning should also be helpful for the development of antivirals.

Glucose-regulated protein 78

We previously found that glucose-regulated protein 78 (GRP78) is an antiviral target for HAV (Table 1)[50-52]. Computational drug discovery using the structure of HAV and GRP78 may lead to the discovery of new anti-HAV drugs or drug repositioning and drug repurposing for anti-HAV drugs[68-71].

CONCLUSION

We found that several drugs potentially inhibit HAV IRES-dependent translation and HAV replication. Approaches that utilize AI, machine learning and deep learning methods could have the most promise in the discovery of new anti-HAV drugs. A systematic approach based on big data mining with AI is also useful for the development of anti-HAV drugs[71].

Table 1 Target and mechanism of anti-hepatitis A virus candidates

Target or mechanism	Drug	Ref.
La antigen	SD-1029, AG490	Jiang *et al*[34]
JAK2-STAT3	AZD1480	Jiang *et al*[35]
GRP78	Japanese rice-koji miso extracts	Shubin *et al*[50]; Choi *et al*[51]
GRP78	Zinc sulfate	Ogawa *et al*[52]
Inflammatory cytokines	Zinc chloride	Mo *et al*[53]

La: Lupus La protein/SSB; JAK: Janus kinase; STAT: Signal transducer and activator of transcription; GRP78: Glucose-regulated protein 78.

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