Review Article

DDX5: an expectable treater for viral infection- a literature review

Minghui Hu[1#], Hongying Zheng[1#], Jingqi Wu[2], Yue Sun[3], Tianying Wang[4], Shuang Chen[5]

[1]Clinical Lab, The Affiliated Hospital of Qingdao University, Qingdao China; [2]Microbiology Department, Harbin Medical University, Harbin, China; [3]School of Public Health, Harbin Medical University, Harbin, China; [4]Clinical Research Center, Qingdao Municipal Hospital, Qingdao, China; [5]Clinical Lab, Qingdao Municipal Hospital, Qingdao, China

Contributions: (I) Conception and design: T Wang, S Chen; (II) Administrative support: T Wang; (III) Provision of study materials or patients: M Hu, H Zheng; (IV) Collection and assembly of data: J Wu, Y Sun; (V) Data analysis and interpretation: M Hu, H Zheng, J Wu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Tianying Wang. Clinical Research Center, Qingdao Municipal Hospital, No. 5 Donghai Middle Road, Shinan District, Qingdao 266071, China. Email: wangty0929@163.com; Shuang Chen. Clinical Lab, Qingdao Municipal Hospital, Qingdao, No. 1 Jiaozhou Road, Shibei District, Qingdao 266011, China. Email: csman1986@126.com.

Background and Objective: DEAD-box protein (DDX)5 plays important roles in multiple aspects of cellular processes that require modulating RNA structure. Alongside the canonical role of DDX5 in RNA metabolism, many reports have shown that DDX5 influences viral infection by directly interacting with viral proteins. However, the functional role of DDX5 in virus-associated cancers, as well as the identity of DDX5 in virus infection-associated signaling pathways, has remained largely unexplained. Here, we further explore the precise functions of DDX5 and its potential targets for antiviral treatment.

Methods: We searched the PubMed and PMC databases to identify studies on role of DDXs, especially DDX5, during various viral infection published up to May 2022.

Key Content and Findings: DDX5 functions as both a viral infection helper and inhibitor, which depends on virus type. DDXs proteins have been identified to play roles on multiple aspects covering RNA metabolism and function.

Conclusions: DDX5 influences viral pathogenesis by participating in viral replication and multiple viral infection-related signaling pathways, it also plays a double-edge sword role under different viral infection conditions. Deep investigation into the mechanism of DDX5 modulating immune response in host cells revealed that it holds highly potential usage for future antiviral therapy. We reviewed current studies to provide a comprehensive update of the role of DDX5 in viral infection.

Keywords: DEAD-box proteins (DDXs); viral infection; cellular processes; antiviral target

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Introduction

The DEAD-box subfamily of RNA helicases is distinguished by the presence of several conserved motifs, including the signature Asp-Glu-Ala-Asp (D-E-A-D) sequence that gives rise to their name. These proteins have been shown to play crucial roles covering multi-aspect of RNA metabolism and function, including transcription; RNA processing; ribosome biogenesis; RNA exportation and turnover; translation and messenger RNA (mRNA) degradation; and processes participating in ribonucleoprotein (RNP) complex association or dissociation, and also the modulation of RNA structure (1,2). The *DDX5* (*p68*) gene is a prototypic member of the DDX RNA helicases that encompasses multiple cellular functions (3) and is responsible for multiple steps of RNA metabolism from post-transcriptional regulation to ribosome biogenesis (3), while also involving in many cellular processes, some of

Table 1 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	Started searching from March 1, 2020
Databases and other sources searched	PubMed, PMC databases
Search terms used (including MeSH and free text search terms and filters)	"DDX", "DDX and virus", "DDX and antiviral", "DDX5 and virus"
Timeframe	From March 1, 1991 to May 31, 2022
Inclusion and exclusion criteria (study type, language restrictions etc.)	English
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	All the authors involved in literature selection independently, and papers were gathered to be screened. According to the relevance of the content, we selected the reference which represented for the general views and newly concepts and discoveries
Any additional considerations, if applicable	None

which are independent of its RNA helicase activity. Various studies have focused on the roles of DEAD-box protein 5 (DDX5) in cellular life cycle regulatory, tumor genesis and development, and spermatogenesis (4-8). Furthermore, DDX5 plays an important role in viral pathogenesis related to its transcriptional regulatory function. Several viruses have learned to manipulate DDX5 through a range of strategies to favor their own replication in the host cells. Viral infection is a sophisticated process assisted by multiple cellular responses (9).

Many signaling pathways have been confirmed to regulate viral infection-induced host responses. However, among current studies on the participation of DDX5 in viral infection-associated cellular responses, whether and how DDX5 impacts viral infection-associated signaling pathways, has remained largely unexplored. Herein, we reviewed current evidence demonstrating viral infection-related signaling pathway and the role of DDX5 on viral infection. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2375/rc).

Methods

In our study, we primary focus on the role of DDXs played on viral infection processes. Literatures searching was performed in PubMed and PMC databases. Papers were considered regardless of year of publication. The following searching key words were used in [tittle/abstract]: "DDX" OR "DDX AND VIRUS" OR "DDX AND ANTIVIRAL" OR "DDX5 AND VIRUS". We also broaden the scope of research by reviewing work on related aspects. Following the search, all identified referable studies were collected. The search strategy summary is shown in *Table 1*.

The role of DDXs on antiviral innate immunity

For DDX5, its potential role on antiviral innate immunity remains is still complicated and confusing. Recently, Xu *et al.* (10) found that DDX5 plays negative effect on innate immunity. It promotes antiviral transcripts methylation facilitates viral propagation. They identified the DDX5-bound RNAs, including DEXH (Asp-Glu-X-His) box polypeptide 58 (DHX58), p65, and nuclear factor-κB (IκB) kinase (IKK)-γ. Furthermore, DDX5 showed the regulatory role on m6A RNA methylation and further block the DHX58-TBK1 and p65 pathways to dampen antiviral immunity system in vesicular stomatitis virus (VSV)-infected cells. The regulatory process of m6A modification is dynamic and reversible, which is composed of "writers," "erasers," and "readers." catalytic subunit METTL3 and cofactors like METTL14 and WTAP composed m6A writers (11). m6A erasers composed by FTO and ALKBH5, could reversibly erase the regulation. The modification is followed by the functionally interpretation depends on the binding of m6A readers. The cytoplasmic YTH domain family proteins could directly recognize and bind with m6A, which mediated downstream cellular processes, including mRNA decay and translation efficiency (12-14). Zhao *et al.* recently elucidated that the DDX5/METTL3-METTL14/YTHDF2 signaling axis regulated *IFN-β*, *IL-6*, and *DHX58* mRNAs, which participated in regulating the innate

immunity response to influenza virus infection (15). All above indicates DDX5 might be a potential valuable target for prohibiting viral immune evasion.

DDX is the largest family of RNA helicases that regulate RNA biogenesis by unwinding short RNA duplexes. It has been demonstrated that nuclear DDX46 played a negative role on antiviral innate responses by binding ALKBH5 (eraser) and inducing retention of Mavs, Traf3 and Traf6 transcripts (16). DDX46 is also a part of the 17S U2 small nuclear ribonucleic particle complex, which plays an essential role in RNA splicing and assembly (17,18). Moreover, Coronaviruses have been found to hijacked DDX and taken part in DDX-mediated viral replication (19). Some work as cytoplasmic sensors of viral RNA, while others collaborate with other proteins (20,21). DDX1 has been reported to be assembled into multiprotein complexes through innate immunity regulatory, in which SPRY a protein interaction module was participated (22). A directly interaction of N protein has also been confirmed between DDX21 and SARS-CoV-2 (23). However, the mechanism on viral replication is still unclear. DDX3X is found to be recruited to the IFN promoter (24), and be component of the RIG-I sensor complex which involving the recognition of viral genome, the IFN activation (25,26) and the NF-κB inflammatory response (27). In summarize, Human DDXs play important roles in variety biological processes and present multiple characters between virus-host communication.

Viral infection-related signaling pathway

Metabolism and immune responses are 2 fundamental biological processes that serve to protect the host from sophisticated viral pathogeneses. Viruses employ diverse strategies to recruit metabolism while inactivating immune responses to attain maximal reproduction or persistent infection within the host (9). Various molecular signaling pathways, such as STAT3, Notch, NF-κB, Wnt, and mTOR, participate during viral infection and mediate various cellular responses. For example, the role of STAT3 in viral replication is apparently complex, due to its double-edged roles in viral infections, which depends on the type of virus. According to type of viral infection, STAT3 functions as a pro-viral factor during hepatitis B virus (HBV), hepatitis C virus (HCV), Epstein-Barr virus (EBV), human immunodeficiency virus 1 (HIV-1), and so on; while as an anti-viral factor during influenza virus A (IVA) and human metapneumovirus (hMPV) infections (28). Japanese Encaphalitis virus (JEV) has been shown to induce cell apoptosis by inhibiting the STAT3-Foxo-Bcl-6/p21 pathway (29). Norovirus is a major cause of gastroenteritis worldwide, which could induce the innate immune response in human intestinal epithelial cells. Its replication could be restricted by the activation of IFN-induced JAK/STAT signaling pathway (29). Recently, the Notch signaling pathway has been identified in the immune modulating responses induced by the infection of many viruses, such as porcine reproductive and respiratory syndrome virus (PRRSV) infection (30) respiratory syncytial virus (RSV) (31), and enterovirus 71 (32). Activation of the nuclear factor (NF)-κB signaling pathway plays essential roles in the regulation of immune responses to pathogenic infection. Viral pathogens could manipulate NF-κB activation pathways to avoid cellular antiviral responses (33,34), such as poxvirus (35), HIV (36), PRRSV (37), and IV (38). Thereby, inhibition of NF-κB activation provided inspiration for the development of effective therapeutic strategies. A recent study found that the erucic acid, which was isolated from the Isatis indigotica Fort. (Ban lan gen), suppresses influenza A virus (IAV) viral replication and inflammation through modulation of NF-κB and p38 MAPK pathway, which may be associated with anti-influenza virus efficacy (39). The Wnt signaling pathway is a key network susceptible to viral manipulation, especially by tumor associated viruses. A study suggested that replication of the influenza virus can be regulated by Wnt/β-catenin signaling, and IAV infection can be repressed by miR-193b via inhibition of Wnt/β-catenin signaling (40). Furthermore, the study demonstrated that the HIV accessory protein Vpu downregulates the formation of peroxisome, which plays an important role in innate immune signaling and central nervous system function, by regulating the Wnt/β-catenin pathway (40). Cellular stress caused by viral infection can both activate and suppress the mTOR signaling pathway. On the one hand, autophagy is a threat to many viruses because the host cells rely on the mTORC1 pathway and autophagy to fight against viral replication and transmission. On the other hand, viruses hijack mTOR as a strategy to favor their replication (41,42). Infection with HIV-1 induces the inhibition of mTORC1 in CD4 T cells at the early phase of infection to limit viral spread, while the mTORC1 is actively modulated by viral proteins at the late stage to accelerate viral replication and the generation of new virions (11). Infection with PRRSV activates the mTOR/autophagy pathway in a manner that allows for efficient replication while avoiding associated clearance mechanisms (43). More comprehensive knowledge of the role of mTOR signaling

Table 2 Double-edge roles of DDX5 (Dead-box family 5) on various virus types

DDX5 Role	Genome	Virus	Pathway	Effect of DDX5 on virus infection	Reference
Inhibitor	dsDNA	HBV	HBV minichromosome	Knockdown of DDX5 enhanced the RNA transcription from the HBV minichromosome	(48)
	dsDNA	MYXV	–	Downregulation of DDX5 enhanced MYXV replication, MYXV foci size, and virus spread	(49)
	+ssRNA	CSFV	NS5A	Remains unknown	(50-52)
	+ssRNA	DTMUV	–	Remains unclear	(53,54)
	dsDNA	EBV	EBNA2	Antiviral effects; Serve as methylation substrate	(55,56)
Helper	Retrovirus	HIV-1	Rev	Facilitates Rev/RRE-mediated nuclear export of HIV-1 transcripts [24]	(57)
			Tat	Participates in the transcription elongation process of the integrated HIV-1 provirus	(58)
	+ssRNA	HCV	CRE	Promotes HCV IRES translation	(59)
			NS5B	Enhances viral RNA transcription	(60)
	+ssRNA	JEV	3'UTR	Promotes viral RNA replication	(61)
	-ssRNA	IVA	Viral polymerase	Remains unclear	(62)
	+ssRNA	Porcine reproductive and respiratory syndrome virus (PRRSV)	Nsp9	Promotes virus replication	(63)
	+ssRNA	Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)	Nsp13	Promotes virus replication	(64)

DDX5, DEAD-box protein 5; dsDNA, double-stranded DNA; ssRNA, single-stranded RNA; HBV, hepatitis B virus; MYXV, myxoma virus; CSFV, classical swine fever virus; DTMUV, Duck Tembusu virus; EBV, Epstein-Barr virus; HIV-1, human immunodeficiency virus type 1; HCV, hepatitis C virus; JEV, Japanese encephalitis virus; IAV, influenza A virus.

responses during different viral infections may provide new drug targets for antiviral therapeutic intervention strategies.

The multiple roles of DDX5 in viral infection

The whole life cycle of viruses, from viral entry to release, is benefit from the host and contributes to the interactions between viral and host factors (44). Viral infection-induced movements of host and viral proteins events promote localization-dependent protein interactions and alterations to protein functions that contribute to either host antiviral responses or viral replication (45). Most members of the DDX helicase family, including DDX5, have been shown play diverse roles during viral infections (46,47). In current reports, DDX5 functions as both a viral infection helper and inhibitor, which depends on virus type (*Table 2*). Some viruses require active DDX5 for efficient viral replication through direct interaction with viral proteins, including HIV-1, HCV, severe acute respiratory syndrome coronavirus (SARS-CoV), JEV, PRRSV, and IVA, while others require inhibition of DDX5 activity, including the HBV and myxoma virus (MYXV). It has also been implicated in the translation of HCV through interaction with the HCV genome. Several reports (50,53,65) have identified the participation of DDX5 during viral infection, including EBV, classical swine fever virus (CSFV), and Duck Tembusu virus (DTMUV). The interplay between DDX5 and the viral life cycle has scarcely been reported, and the knowledge of the underlying mechanisms of DDX5 activity during the time course of infection remains limited.

DDX5 acts as a viral infection helper

HIV-1

The virus known as HIV-1 interacts with numerous cellular proteins during infection, including helicases. The virus does not encode a helicase, while it interacts with helicases via either viral RNA or proteins. Many helicases have been identified as cellular factors that affect HIV-1 replication (66). Several DDX members, such as DDX3 (67,68), DDX21 (69), and DDX5 (70), have been reported to play important roles in the HIV-1 life cycle. The HIV-1 genome encodes 3 structural proteins, Gag (group-specific antigen), Pol (polymerase), and Env (envelope), the accessory proteins, Vif, Vpu, Vpr, and Nef, and the regulatory proteins, Tat and Rev (71). Like all retroviruses, in infected cells, the single positive-sense strand genomic RNA of HIV-1 is converted to double-strand DNA and integrates into the genome of the target cell. The integrated DNA is transcribed along with cellular DNA and generates a large volume of spliced, un-spliced, or incompletely spliced viral mRNAs in the nucleus (72). The Rev protein serves as a key regulator in the late phase of HIV-1 replication through binding to Rev response element (RRE) on un-spliced and incompletely spliced transcripts and drives their translocation from the nucleus to the cytoplasm in a chromosomal maintenance 1 (CRM1)-dependent manner (73). Both DDX1 (74) and DDX3 (68) have previously been defined as co-factors to modulate Rev function. Proteomics and statistical analysis have been employed to identify a set of host cell factors that interact with Rev. Among which, downregulation of the DDX3X, DDX5, DDX17, and DDX21 showed distinctive effects on multiple features of HIV replication (75). Like DDX1 and DDX3, DDX5 has also been confirmed to serve as a co-factor of HIV-1 Rev to facilitate nuclear export of HIV-1 transcripts (57). In addition, DDX5 has been found to cooperate with DDX3 in this process (76). As a well-known heterodimerization partner of DDX5 in the cell, DDX17 has been implicated as involved in several aspects of HIV replication including interaction with HIV-1 Rev (75) and to promote the production of HIV-1 infectious particles by modulating Gag processing and genomic RNA packaging (77). Recently, it was found that DDX17 interacts with essential splicing factors to regulate the production of HIV-spliced transcripts independently of DDX5 (78,79). Previous research has revealed that DDX3 directly interacts with HIV-1 Tat protein to facilitate viral mRNA translation (67). A recent study demonstrated that DDX5 also participates in the transcription elongation process of the integrated HIV-1 provirus as a co-factor of Tat. In normal conditions, activated p-TEFb is bound with HEXIM1/2 complex. It was found that DDX5 can interact with Tat and may potentiate the availability of p-TEFb through sequestering HEXIM1. This activity is unique to DDX5 and cannot be replaced by DDX17, which suggests that members of DDXs could play different effects on HIV (58).

HCV

Although the HCV encodes its RNA helicases (NS3), several members of the DDXs have been found to participate in HCV replication, including DDX3, DDX5, and DDX6. Among them, DDX5 has been speculated to play a role in viral production at the late stage of the HCV life cycle (80). Infection with HCV is associated with hepatitis, which often develops into malignant chronic diseases, including liver cirrhosis and hepatocellular carcinoma (HCC) (81). While HCV belongs to the family *Flaviviridae*, +ssRNA virus. It has been identified that DDX5 is a candidate cellular protein that influences viral genome translation and replication by recruiting proteins and RNA-RNA interaction. It was found that DDX5 is required for full HCV IRES translation through interacting with CRE, as knockdown of DDX5 led to inhibition of HCV IRES activity (59). The viral protein NS5B could specifically recognized the motifs in 3'UTR—which is responsible for the synthesis of +/– strand HCV RNA—and has emerged as an attractive antiviral target for HCV (60). It was found that the C terminus of NS5B is important for DDX5 and NS5B interaction which enhances viral RNA transcription (60). A subsequent study found that DDX5 also can interact with the N terminus of NS5B, and while the 2 binding sites are different, their interaction is auto-inhibited by the structural elements in the N-terminal region (NTR) of the N-terminal fragment of DDX5 (82). The study found that siDDX5 causes the decreased expression of HCV RNA in cells transfected with full-length HCV expression vector (Q19) (60). The experiments were also carried out in HCV stably transfected cell lines, and luciferase assay examination suggested that knockdown of DDX5 decreases virus production (83). The issue of whether DDX5 contributes to the regulation of the HCV life cycle by interacting with other HCV proteins remains uncertain, and more studies are needed.

JEV

While DDX5 was found to recruit from the nucleus to the cytoplasm during JEV infection, it was also identified as a positive regulator in the JEV replication due to its helicase activity (84). Japanese encephalitis (JE) is a severe mosquito-borne zoonotic disease caused by JEV (85), which is a single-stranded positive-sense RNA virus that belongs to the genus *Flavivirus* of the family *Flaviviridae*. The genome of JEV encoding 3 structural proteins and 7 non-structural proteins is in the order of prM-E-NS1-NS2a-NS2b-NS3-NS4a-NS4b-NS5 from 5' to 3' (86). Both NS5 and NS3 proteins are likely involved in negative-strand RNA synthesis through the formation of a replication complex with the 3'UTR of positive-strand RNA. The study confirmed that DDX5 involves in viral RNA replication by binding to the JEV 3'UTR. Furthermore, DDX5 was shown to interact and colocalize with the NS3, NS5, and C proteins in the cytoplasm of infected cells (84).

IAV

There are A, B, and C types of influenza viruses, among IAV are the most virulent of the 3 types, and can infect a wide range of avian and mammalian hosts (87). Some of the DDX have been identified as cellular factors involved in IAV infection by interacting with the polymerase of IAV, such as DDX19, DDX5, and DDX17. The IAV is a negative-sense RNA virus of the *Orthomyxoviridae* family. The negative-sense RNA genome of IAV needs to be converted to positive-sense to serve as a template for successful transcription and viral protein translation. For the initiation of RNA synthesis, the viral ribonucleoprotein (vRNP) complex, which composed of the viral genome, RNA polymerase (PA, PB1, and PB2), and nucleoprotein (NP), are translocated to the nucleus and behaves as a viral RNA synthesis template. Before assembly into progeny virions, the vRNPs export with viral RNA from the nucleus to the cytoplasm in a CRM1-dependent manner mediated by NP binding to CRM1 (88). A study found that DDX19 associated with the viral polymerase modulated by its ATPase activity. The viral polymerase recruits DDX19 to enhance the nuclear export of viral mRNAs in IAV infected cells (89). Meanwhile, DDX5 was also identified as a member of the cellular factors able to interact with the viral polymerase. Experimental results have demonstrated that DDX5 and DDX17 are required for influenza viral polymerase activity (62). Additionally, DDX17 was found to facilitate efficient human-adapted H5N1 virus RNA synthesis in human cells. It has also been found that DDX17 colocalizes with NP in the cell nucleus early and redistributes in the cytoplasm late during infection, which suggests that it may involve in vRNP nuclear export in a CRM1-dependent manner (62). The roles of DDX5 and DDX17 in IAV infection need to be further investigated.

PRRSVs

It was found that DDX5 functions as a positive regulator of PRRSV replication. The PRRSV belongs to the genus *Arterivirus* of the family *Arteriviridae*. The genome of PRRSV is a +ssRNA, which contains 9 open ORFs that encode for the viral nonstructural and structural proteins. The ORF1a and ORF1b located in its 5'end encode the polyproteins pp1a and pp1ab, respectively. The pp1a is processed in 9 nonstructural proteins (Nsps). The Nsp9 to Nsp12 are produced by proteolytic cleavage of pp1ab and are recognized as being involved in viral genome transcription and replication. Among them, Nsp9 and Nsp10 have been recognized as crucial enzymes in arterivirus RNA synthesis. The Nsp9 contains an RdRp domain in its C-terminal portion and serves as the catalytic subunit of the viral replication/transcription complex (90-92). Meanwhile, Nsp10 is required for RNA synthesis as viral RNA helicase (91,92). It has been reported that Nsp9 and Nsp10 together contribute to generation of the enhanced replication efficiency and virulence of highly pathogenic PRRSV (HP-PRRSV) (93). More recently, DDX5 was identified as a cellular protein interacting with the Nsp9 of PRRSV. The study revealed that DDX5 serves as a PRRSV replication positive regulator by colocalizing and interacting with viral Nsp9. Besides, knockdown of the DDX5 gene inhibited the PRRSV replication, while the overexpression of DDX5 promoted it. There have been 2 domains, N-terminal DDX5 domains, DExDc (DExD/H box-containing domain) and HELICc (helicase superfamily C-terminal), identified as serving as the binding regions with the RdRp domain of Nsp9 (63). These findings suggest that DDX5 plays an important role in PRRSV replication.

SARS-CoV

Coronaviruses (CoVs) are categorized into four genera including Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus (94). It has been found that DDX5 serves as a cellular cofactor of the

SARS-CoV helicase and involves in the viral replication of SARS-CoV (64). The SARS-CoV was identified as the pathogen of a global outbreak of severe acute respiratory syndrome (SARS) in 2003. The SARS-CoV contains a very large _+ssRNA genome that encodes 4 structural proteins: the spike protein, the membrane protein, the envelope protein, and nucleocapsid protein (abbreviated to S, M, E, and N, respectively); 2 large polyproteins: pp1a and pp1ab, which are cleaved into 16 Nsps (from Nsp1 to Nsp16); and a group of accessory proteins. (95-97). Many of the Nsps are responsible for viral RNA synthesis through their participation in the formation of replication and transcription complex (RTC) and exert their enzyme activities (95). The CoV Nsp13 encodes the RNA helicase domain (95,96), and has been identified as a potential drug target (98). Furthermore, it has been revealed that the Nsp12 (RdRp) can enhance the helicase activity of SARS-CoV Nsp13 by directly interacting with it (99). The study revealed that DDX5 can interact with the SARS-CoV Nsp13 in the human A549 cell line. In addition, the decrease of DDX5 results in the uppression of viral replication (64). A novel member of human CoV, belonging to Betacoronavirus and named as SARS-CoV-2, has recently emerged, causing the major outbreak of coronavirus disease 2019 (COVID-19) epidemic worldwide. The SARS-CoV-2 has been identified as genetically related to SARS-CoV but it holds higher infectivity to human beings than the others, including the SARS-CoV and the Middle East respiratory syndrome virus (MERS) (94,100). To date, no specific therapy has been demonstrated as available for use against COVID-19. In the research of SARS-CoV-2 druggable targets, computational drug discovery methods have revealed potential drug candidates against the Nsp12 polymerase and Nsp13 helicase (101). A report discussed that SARS-CoV-2 helicase inhibitor may exert antiviral activity and might bring a potential therapeutic strategy to tackle the COVID-19 pandemic (102). These studies remind us that the CoV viral proteins may serve as important therapeutic targets. As a cellular cofactor of SARS-CoV helicase, the precise cellular effects exerted by DDX5 remain largely unexplored and need further study.

DDX5 Acts as a viral infection inhibitor

HBV

The DDX5 also exerts functions in inhibiting viral infection processes, including the HBV and MYXV. The HBV is a member of the *hepadnaviridae* family that productively infect hepatocytes and is a prototype of a family of small DNA viruses that contains a double-stranded DNA genome. In infected hepatocytes, the genome of HBV converts to a covalently closed circular DNA (cccDNA) in the nucleus. The cccDNA is organized into a minichromosome to serve as the template for the synthesis of all viral mRNAs (103). It was shown that knockdown of DDX5 enhanced the RNA transcription from the HBV minichromosome (48), which suggests DDX5 may function as an inhibitor of HBV infection. Moreover, chronic HBV infection is a major cause of HCC; DDX5 also plays an important role in poor prognosis HBV-associated HCC (48). However, the knowledge of the role of DDX5 in HBV infection is still incomplete and further investigation of the mechanism by which DDX5 inhibits HBV infection may be significant for antiviral and anticancer treatment.

MYXV

The DDX5 was identified as one of the DDX RNA helicases that inhibit MYXV replication. The MYXV is the prototypic member of the *Leporipoxvirus* genus of the *Poxviridae* family of DNA viruses that contains a large double-strand DNA genome. While MYXV infects only rabbits and causes a highly lethal systemic disease called myxomatosis in European rabbit, it exerts a nonpathogenic effect on humans. However, MYXY can selectively infect and kill human cancer cells by direct oncolysis and/or enhance the host anti-tumor immune responses (104). The MYXV tropism for cancer cells is identified to be associated with multiple cellular signaling pathways that involving viral replication and host antiviral immune responses (49). Several members of DExD/H RNA helicases, including DDX5, have been found to play crucial regulatory roles that are associated with MYXV tropism for selective cancers. Among them, 5 host RNA helicases (DDX3X, DDX5, DHX9, DHX37, DDX52) have been identified as anti-viral host factors, while the other three helicases, that is DHX29, DHX35, and RIG-I, have been identified as promoting factors to virus in host (49). The downregulation of DDX5 has been shown to enhance MYXV replication, MYXV foci size, and viral spread, which suggesting that DDX5 may act as double-edge sward during MYXV infection (49). However, the function of DDX5 in multiple pathways of antiviral defense responses of the host cell and the specific molecular mechanism has not been further characterized.

Identification of DDX5 in other viral infections

CSFV

The CSFV is the pathogen of classical swine fever (CSF) in porcine species. Like HCV, The CSFV is also a member of the *Flaviviridae* family. The CSFV NS5A shares a similar N-terminal C2717-C2740-C2742-C2767 zinc finger domain (NTD) with HCV NS5A, and this domain is required for CSFV replication (50-52). It was found that CSFV NS5A protein might modulate CSFV replication through concentration changes. Further study demonstrated that the CSFV NS5A regulates viral RNA synthesis and viral replication by interacting with both the 3'UTR and NS5B (50). Meanwhile, DDX5 was identified as one of the CSFV NS5A interactive proteins via yeast 2-hybrid analysis in the complementary DNA (cDNA) library of the swine umbilical vein endothelial cell (SUVEC) (105). However, the underlying mechanisms of DDX5 activity in CSFV infection remain unelucidated.

DTMUV

The DTMUV is another member of the *Flaviviridae* family, which has caused huge economic losses to the duck industry in China since 2010 (53). A recent study identified 192 differentially expressed cellular proteins after DTMUV infection by the iTRAQ-based proteomic approach. The validation results confirmed that both DDX5 and DDX3X are downregulated at 48 hours after infection. Furthermore, it was found that DDX3X could inhibit DTMUV replication by modulating the type I interferon (IFN) pathway via TBK1 (53). Also, a recent study confirmed that the duck DDX3X played an essential role in defense against TMUV infection by modulating type I IFN (54). However, the exact role of DDX5 in DTMUV infection remains unclear.

EBV

The Epstein-Barr virus (EBV) is a human oncogenic herpesvirus that establishes lifelong latent infection in the host and is linked to several human tumors, such as lymphoma, nasopharyngeal carcinoma, and gastric cancer (106). The EBV-encoded nuclear antigen 2 (EBNA2) is a transcription factor that modulates EBV-latent gene transcription and enhances the expression of many cellular genes that control cell growth and survival. The EBNA2 and its coactivator have also been shown to contribute to EBV-mediated B-cell growth transformation (107). It contains a feature arginine-glycine (RG) repeat that is essential for the transformation of lymphocytes (55). A recent study confirmed that EBNA2 contains mono-methylated arginine (MMA) residues within the RG repeat and identified many interactive proteins of EBNA2, including DDX5 (56), which share similar RG repeat elements and MMA residues with those in EBNA2 (108), and may serve as methylation substrate (56). These findings suggest that DDX5 may function as a potential cellular protein targeted by EBNA2 during the transformation of B-cells (56).

Discussion

The DDX5 is a multifunctional molecule playing an important role in a number of cellular processes. The functions of DDX5 as a transcriptional coactivator enable its important roles in viral infection. Much attention has been given to DDX5 in antiviral research due to its involvement in the replication of several viruses. On the one hand, DDX5 is required to facilitate both the export of mis-spliced HIV RNA transport and also take part in the transcription elongation of the integrated HIV-1 provirus through interacting with Tat. Inhibition of DDX5 blocks the replication of HIV, HCV, JEV, IVA, and some other viruses. On the other hand, DDX5 displays antiviral effects against HBV and MYXV, while the specific molecular mechanisms are still largely unknown. The virus-host interactions important for the viral life cycle can be used as antiviral targets of drugs (44,109). The coactivator role of DDX5 in viral infection suggests that it has the potential to serve as an optional antiviral target. However, current studies on the functions of DDX5 in viral infection appear to rely on direct interactions between DDX5 and viral proteins. Environmental stresses threatening cellular homeostasis and trigger various cellular responses such as activation of immune responses, cell survival pathways, apoptosis, autophagy. Several DExD/H RNA helicases have been shown to contribute to intracellular antiviral responses (110). Both RIG-I and MDA-5 contain amino-terminal caspase activation and recruitment domains (CARDs), which are responsible for downstream IFN signaling (46,110,111). In addition, several DDX helicases that lack the CARDs also promote interferon induction or other inflammatory responses, such as DDX1, DDX21, DHX36, DDX41, DDX3X, DDX60, and DDX60L. Although it is clear that DDX3X also serves as a negative

regulator of interferon responses (46), the role of DDX5 in cellular innate immunity has not yet been defined. To ensure successful viral replication, viruses have manipulated diverse strategies to activate metabolism, while inactivating immune responses (9). Various viruses have evolved strategies to disturb cellular defense, not only by developing process but also by encoding miRNAs involved in virus-associated tumorigenesis (112). Furthermore, host miRNAs may participate in host-virus interactions, influencing viral replication (113). Although the multifaceted roles of DDX5 have been identified in different cancer-related cellular processes, it is not yet clear whether and how DDX5 participates in viral infection-related cellular responses. To further the understanding of the mechanisms of DDX5 influence on viral infection, we have summarized the viral infection-related signaling pathways and the role of DDX5 in viral infection, and, taking into consideration the fact that viral infection and pathogenesis are modulated by multiple cellular signaling pathways, we cannot exclude that DDX5 may also influence viral pathogenesis through participating in viral infection-related signaling pathways. Moreover, DDX5 is a barrier for somatic cell reprogramming throughout the entire process (114). DDX5 lost the regulatory function on the non-canonical PRC1 mediated by miR125b, which could result in ubiquitination and repression of histone H2A (61). Inactive DDX5 enhances reprogramming efficiency by erasing their m6A modification, which is usually required for nucleus-transportation and translation (114,115). Further investigation of the mechanism of DDX5 in viral infection are highly significant for future antiviral therapy.

Conclusions

In this review, we deduce that DDX5 is an important potential antiviral target. While DDX5 influences viral pathogenesis by participating in viral replication and multiple viral infection-related signaling pathways, it also plays a double-edge sword role under different viral infection conditions. Deep investigation into the mechanism of DDX5 modulating immune response in host cells revealed that it holds highly potential usage for future antiviral therapy.

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Footnote

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References

1. Su C, Tang YD, Zheng C. DExD/H-box helicases: multifunctional regulators in antiviral innate immunity. Cell Mol Life Sci 2021;79:2.
2. Cargill M, Venkataraman R, Lee S. DEAD-Box RNA Helicases and Genome Stability. Genes (Basel) 2021;12:1471.
3. Onomoto K, Onoguchi K, Yoneyama M. Regulation of RIG-I-like receptor-mediated signaling: interaction between host and viral factors. Cell Mol Immunol 2021;18:539-55.
4. Giraud G, Terrone S, Bourgeois CF. Functions of DEAD box RNA helicases DDX5 and DDX17 in chromatin organization and transcriptional regulation. BMB Rep 2018;51:613-22.
5. Hashemi V, Masjedi A, Hazhir-Karzar B, et al. The

role of DEAD-box RNA helicase p68 (DDX5) in the development and treatment of breast cancer. J Cell Physiol 2019;234:5478-87.
6. Nyamao RM, Wu J, Yu L, et al. Roles of DDX5 in the tumorigenesis, proliferation, differentiation, metastasis and pathway regulation of human malignancies. Biochim Biophys Acta Rev Cancer 2019;1871:85-98.
7. Legrand JMD, Chan AL, La HM, et al. DDX5 plays essential transcriptional and post-transcriptional roles in the maintenance and function of spermatogonia. Nat Commun 2019;10:2278.
8. Cho M, Lee E, Shon J, et al. Induction of DEAD Box helicase 5 in early adipogenesis is regulated by Ten-eleven translocation 2. Biochim Biophys Acta Mol Cell Biol Lipids 2020;1865:158684.
9. Zhang S, Carriere J, Lin X, et al. Interplay between Cellular Metabolism and Cytokine Responses during Viral Infection. Viruses 2018;10:521.
10. Xu J, Cai Y, Ma Z, et al. The RNA helicase DDX5 promotes viral infection via regulating N6-methyladenosine levels on the DHX58 and NFκB transcripts to dampen antiviral innate immunity. PLoS Pathog 2021;17:e1009530.
11. Akbay B, Shmakova A, Vassetzky Y, et al. Modulation of mTORC1 Signaling Pathway by HIV-1. Cells 2020;9:1090.
12. Roundtree IA, Luo GZ, Zhang Z, et al. YTHDC1 mediates nuclear export of N6-methyladenosine methylated mRNAs. Elife 2017;6:31311.
13. Hazra D, Chapat C, Graille M. m6A mRNA Destiny: Chained to the rhYTHm by the YTH-Containing Proteins. Genes (Basel) 2019;10:49.
14. Lesbirel S, Wilson SA. The m(6)Amethylase complex and mRNA export. Biochim Biophys Acta Gene Regul Mech 2019;1862:319-28.
15. Zhao L, Zhao Y, Liu Q, et al. DDX5/METTL3-METTL14/YTHDF2 Axis Regulates Replication of Influenza A Virus. Microbiol Spectr 2022. [Epub ahead of print].
16. Zheng Q, Hou J, Zhou Y, et al. The RNA helicase DDX46 inhibits innate immunity by entrapping m6A-demethylated antiviral transcripts in the nucleus. Nat Immunol 2017;18:1094-103.
17. Cordin O, Beggs JD. RNA helicases in splicing. RNA Biol 2013;10:83-95.
18. Xu YZ, Newnham CM, Kameoka S, et al. Prp5 bridges U1 and U2 snRNPs and enables stable U2 snRNP association with intron RNA. EMBO J 2004;23:376-85.
19. Squeglia F, Romano M, Ruggiero A, et al. Host DDX Helicases as Possible SARS-CoV-2 Proviral Factors: A Structural Overview of Their Hijacking Through Multiple Viral Proteins. Front Chem 2020;8:602162.
20. Zhang Z, Kim T, Bao M, et al. DDX1, DDX21, and DHX36 helicases form a complex with the adaptor molecule TRIF to sense dsRNA in dendritic cells. Immunity 2011;34:866-78.
21. Yoo JS, Kato H, Fujita T. Sensing viral invasion by RIG-I like receptors. Curr Opin Microbiol 2014;20:131-8.
22. D'Cruz AA, Babon JJ, Norton RS, et al. Structure and function of the SPRY/B30.2 domain proteins involved in innate immunity. Protein Sci 2013;22:1-10.
23. Gordon DE, Jang GM, Bouhaddou M, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature 2020;583:459-68.
24. Gu L, Fullam A, Brennan R, Schroder M. Human DEAD box helicase 3 couples IkappaB kinase epsilon to interferon regulatory factor 3 activation. Mol Cell Biol 2013;33:2004-15.
25. Oshiumi H, Sakai K, Matsumoto M, et al. DEAD/H BOX 3 (DDX3) helicase binds the RIG-I adaptor IPS-1 to up-regulate IFN-beta-inducing potential. Eur J Immunol 2010;40:940-8.
26. Gu L, Fullam A, McCormack N, et al. DDX3 directly regulates TRAF3 ubiquitination and acts as a scaffold to co-ordinate assembly of signalling complexes downstream from MAVS. Biochem J 2017;474:571-87.
27. Wang X, Wang R, Luo M, Li C, Wang HX, Huan CC, et al. (DEAD)-box RNA helicase 3 modulates NF-kappaB signal pathway by controlling the phosphorylation of PP2A-C subunit. Oncotarget 2017;8:33197-213.
28. Kuchipudi SV. The Complex Role of STAT3 in Viral Infections. J Immunol Res 2015;2015:272359.
29. Guo F, Yu X, Xu A, et al. Japanese encephalitis virus induces apoptosis by inhibiting Foxo signaling pathway. Vet Microbiol 2018;220:73-82.
30. Lu Y, Zhang Y, Xiang X, et al. Notch signaling contributes to the expression of inflammatory cytokines induced by highly pathogenic porcine reproductive and respiratory syndrome virus (HP-PRRSV) infection in porcine alveolar macrophages. Dev Comp Immunol 2020;108:103690.
31. Ward C, Eger K, Diboll J, et al. Bronchial epithelial cells cultured from clinically stable lung allograft patients promote the development of macrophages from monocytes rather than dendritic cells. Thorax 2009;64:430-5.
32. Hao J, Li P, Tian Y, et al. Crosstalk between Toll-like receptor 3 and Notch signaling contributes to CD14+ monocytes activity in enterovirus 71 infected hand, foot,

and mouth disease. Int Immunopharmacol 2018;60:26-33.
33. Freaney JE, Kim R, Mandhana R, Horvath CM. Extensive cooperation of immune master regulators IRF3 and NFkappaB in RNA Pol II recruitment and pause release in human innate antiviral transcription. Cell Rep. 2013;4(5):959-973.
34. Struzik J, Szulc-Dabrowska L. Manipulation of Non-canonical NF-kappaB Signaling by Non-oncogenic Viruses. Arch Immunol Ther Exp (Warsz). 2019;67(1):41-48.
35. Brady G, Bowie AG. Innate immune activation of NFkappaB and its antagonism by poxviruses. Cytokine Growth Factor Rev. 2014;25(5):611-620.
36. Feng T, Gan J, Qin A, Huang X, Wu N, Hu H, et al. HIV1 downregulates the expression and phosphorylation of receptor tyrosine kinase by targeting the NFkappaB pathway. Mol Med Rep. 2016;14(3):1947-1952.
37. Huang C, Zhang Q, Feng WH. Regulation and evasion of antiviral immune responses by porcine reproductive and respiratory syndrome virus. Virus Res 2015;202:101-11.
38. Kumar N, Xin ZT, Liang Y, et al. NF-kappaB signaling differentially regulates influenza virus RNA synthesis. J Virol 2008;82:9880-9.
39. Liang X, Huang Y, Pan X, Hao Y, Chen X, Jiang H, et al. Erucic acid from Isatis indigotica Fort. suppresses influenza A virus replication and inflammation in vitro and in vivo through modulation of NF-kappaB and p38 MAPK pathway. J Pharm Anal. 2020;10(2):130-146.
40. Xu Z, Lodge R, Power C, et al. The HIV-1 Accessory Protein Vpu Downregulates Peroxisome Biogenesis. mBio 2020;11:03395-19.
41. Le Sage V, Cinti A, Amorim R, et al. Adapting the Stress Response: Viral Subversion of the mTOR Signaling Pathway. Viruses 2016;8:152.
42. Mao J, Lin E, He L, et al. Autophagy and Viral Infection. Adv Exp Med Biol 2019;1209:55-78.
43. Pujhari S, Kryworuchko M, Zakhartchouk AN. Role of phosphatidylinositol-3-kinase (PI3K) and the mammalian target of rapamycin (mTOR) signalling pathways in porcine reproductive and respiratory syndrome virus (PRRSV) replication. Virus Res 2014;194:138-44.
44. Desrochers GF, Pezacki JP. ABPP and Host-Virus Interactions. Curr Top Microbiol Immunol 2019;420:131-54.
45. Cook KC, Cristea IM. Location is everything: protein translocations as a viral infection strategy. Curr Opin Chem Biol 2019;48:34-43.
46. Taschuk F, Cherry S. DEAD-Box Helicases: Sensors, Regulators, and Effectors for Antiviral Defense. Viruses 2020;12:181.
47. Meier-Stephenson V, Mrozowich T, Pham M, et al. DEAD-box helicases: the Yin and Yang roles in viral infections. Biotechnol Genet Eng Rev 2018;34:3-32.
48. Zhang H, Xing Z, Mani SK, et al. RNA helicase DEAD box protein 5 regulates Polycomb repressive complex 2/Hox transcript antisense intergenic RNA function in hepatitis B virus infection and hepatocarcinogenesis. Hepatology 2016;64:1033-48.
49. Rahman MM, Bagdassarian E, Ali MAM, et al. Identification of host DEAD-box RNA helicases that regulate cellular tropism of oncolytic Myxoma virus in human cancer cells. Sci Rep 2017;7:15710.
50. Sheng C, Chen Y, Xiao J, et al. Classical swine fever virus NS5A protein interacts with 3'-untranslated region and regulates viral RNA synthesis. Virus Res 2012;163:636-43.
51. Sheng C, Zhu Z, Yu J, et al. Characterization of NS3, NS5A and NS5B of classical swine fever virus through mutation and complementation analysis. Vet Microbiol 2010;140:72-80.
52. Xu C, Feng L, Chen P, et al. Viperin inhibits classical swine fever virus replication by interacting with viral nonstructural 5A protein. J Med Virol 2020;92:149-60.
53. Sun X, Wang S, Lin X, et al. Proteome analysis of Duck Tembusu virus (DTMUV)-infected BHK-21 cells. Proteomics 2017.
54. Li N, Jiang S, Zhao J, et al. Molecular identification of duck DDX3X and its potential role in response to Tembusu virus. Dev Comp Immunol 2020;106:103599.
55. Barth S, Liss M, Voss MD, et al. Epstein-Barr virus nuclear antigen 2 binds via its methylated arginine-glycine repeat to the survival motor neuron protein. J Virol 2003;77:5008-13.
56. Ayoubian H, Fröhlich T, Pogodski D, et al. Antibodies against the mono-methylated arginine-glycine repeat (MMA-RG) of the Epstein-Barr virus nuclear antigen 2 (EBNA2) identify potential cellular proteins targeted in viral transformation. J Gen Virol 2017;98:2128-42.
57. Zhou X, Luo J, Mills L, et al. DDX5 facilitates HIV-1 replication as a cellular co-factor of Rev. PLoS One 2013;8:e65040.
58. Sithole N, Williams CA, Abbink TEM, et al. DDX5 potentiates HIV-1 transcription as a co-factor of Tat. Retrovirology 2020;17:6.
59. Ríos-Marco P, Romero-López C, Berzal-Herranz A. The cis-acting replication element of the Hepatitis C virus genome recruits host factors that influence viral replication and translation. Sci Rep 2016;6:25729.

60. Goh PY, Tan YJ, Lim SP, et al. Cellular RNA helicase p68 relocalization and interaction with the hepatitis C virus (HCV) NS5B protein and the potential role of p68 in HCV RNA replication. J Virol 2004;78:5288-98.
61. Li H, Lai P, Jia J, et al. RNA Helicase DDX5 Inhibits Reprogramming to Pluripotency by miRNA-Based Repression of RYBP and its PRC1-Dependent and -Independent Functions. Cell Stem Cell 2017;20:571.
62. Bortz E, Westera L, Maamary J, et al. Host- and strain-specific regulation of influenza virus polymerase activity by interacting cellular proteins. mBio 2011;2:e00151-11.
63. Zhao S, Ge X, Wang X, et al. The DEAD-box RNA helicase 5 positively regulates the replication of porcine reproductive and respiratory syndrome virus by interacting with viral Nsp9 in vitro. Virus Res 2015;195:217-24.
64. Chen JY, Chen WN, Poon KM, et al. Interaction between SARS-CoV helicase and a multifunctional cellular protein (Ddx5) revealed by yeast and mammalian cell two-hybrid systems. Arch Virol 2009;154:507-12.
65. Cirone M. EBV and KSHV Infection Dysregulates Autophagy to Optimize Viral Replication, Prevent Immune Recognition and Promote Tumorigenesis. Viruses 2018;10:599.
66. Lorgeoux RP, Guo F, Liang C. From promoting to inhibiting: diverse roles of helicases in HIV-1 Replication. Retrovirology 2012;9:79.
67. Yasuda-Inoue M, Kuroki M, Ariumi Y. DDX3 RNA helicase is required for HIV-1 Tat function. Biochem Biophys Res Commun 2013;441:607-11.
68. Yedavalli VS, Neuveut C, Chi YH, et al. Requirement of DDX3 DEAD box RNA helicase for HIV-1 Rev-RRE export function. Cell 2004;119:381-92.
69. Hammond JA, Zhou L, Lamichhane R, et al. A Survey of DDX21 Activity During Rev/RRE Complex Formation. J Mol Biol 2018;430:537-53.
70. Sithole N, Williams C, Vaughan A, et al. The roles of DEAD box helicases in the life cycle of HIV-1. Lancet 2015;385 Suppl 1:S89.
71. Frankel AD, Young JA. HIV-1: fifteen proteins and an RNA. Annu Rev Biochem 1998;67:1-25.
72. Freed EO. HIV-1 replication. Somat Cell Mol Genet 2001;26:13-33.
73. Kjems J, Askjaer P. Rev protein and its cellular partners. Adv Pharmacol 2000;48:251-98.
74. Edgcomb SP, Carmel AB, Naji S, et al. DDX1 is an RNA-dependent ATPase involved in HIV-1 Rev function and virus replication. J Mol Biol 2012;415:61-74.
75. Naji S, Ambrus G, Cimerman i P, et al. Host cell interactome of HIV-1 Rev includes RNA helicases involved in multiple facets of virus production. Mol Cell Proteomics 2012;11:M111.015313.
76. Yasuda-Inoue M, Kuroki M, Ariumi Y. Distinct DDX DEAD-box RNA helicases cooperate to modulate the HIV-1 Rev function. Biochem Biophys Res Commun 2013;434:803-8.
77. Lorgeoux RP, Pan Q, Le Duff Y, et al. DDX17 promotes the production of infectious HIV-1 particles through modulating viral RNA packaging and translation frameshift. Virology 2013;443:384-92.
78. Sithole N, Williams CA, Vaughan AM, et al. DDX17 Specifically, and Independently of DDX5, Controls Use of the HIV A4/5 Splice Acceptor Cluster and Is Essential for Efficient Replication of HIV. J Mol Biol 2018;430:3111-28.
79. Mancebo HS, Lee G, Flygare J, et al. P-TEFb kinase is required for HIV Tat transcriptional activation in vivo and in vitro. Genes Dev 1997;11:2633-44.
80. Upadya MH, Aweya JJ, Tan YJ. Understanding the interaction of hepatitis C virus with host DEAD-box RNA helicases. World J Gastroenterol 2014;20:2913-26.
81. Takamizawa A, Mori C, Fuke I, et al. Structure and organization of the hepatitis C virus genome isolated from human carriers. J Virol 1991;65:1105-13.
82. Dutta S, Gupta G, Choi YW, et al. The variable N-terminal region of DDX5 contains structural elements and auto-inhibits its interaction with NS5B of hepatitis C virus. Biochem J 2012;446:37-46.
83. Kuroki M, Ariumi Y, Hijikata M, et al. PML tumor suppressor protein is required for HCV production. Biochem Biophys Res Commun 2013;430:592-7.
84. Li C, Ge LL, Li PP, et al. The DEAD-box RNA helicase DDX5 acts as a positive regulator of Japanese encephalitis virus replication by binding to viral 3' UTR. Antiviral Res 2013;100:487-99.
85. Li X, Ma SJ, Liu X, et al. Immunogenicity and safety of currently available Japanese encephalitis vaccines: a systematic review. Hum Vaccin Immunother 2014;10:3579-93.
86. Kukhanova MK, Karpenko IL, Ivanov AV. DEAD-box RNA Helicase DDX3: Functional Properties and Development of DDX3 Inhibitors as Antiviral and Anticancer Drugs. Molecules 2020;25:1015.
87. Shie JJ, Fang JM. Development of effective anti-influenza drugs: congeners and conjugates - a review. J Biomed Sci 2019;26:84.
88. Ampomah PB, Lim LHK. Influenza A virus-induced

apoptosis and virus propagation. Apoptosis 2020;25:1-11.
89. Diot C, Fournier G, Dos Santos M, et al. Influenza A Virus Polymerase Recruits the RNA Helicase DDX19 to Promote the Nuclear Export of Viral mRNAs. Sci Rep 2016;6:33763.
90. Beerens N, Selisko B, Ricagno S, et al. De novo initiation of RNA synthesis by the arterivirus RNA-dependent RNA polymerase. J Virol 2007;81:8384-95.
91. Fang Y, Snijder EJ. The PRRSV replicase: exploring the multifunctionality of an intriguing set of nonstructural proteins. Virus Res 2010;154:61-76.
92. Music N, Gagnon CA. The role of porcine reproductive and respiratory syndrome (PRRS) virus structural and non-structural proteins in virus pathogenesis. Anim Health Res Rev 2010;11:135-63.
93. Li Y, Zhou L, Zhang J, et al. Nsp9 and Nsp10 contribute to the fatal virulence of highly pathogenic porcine reproductive and respiratory syndrome virus emerging in China. PLoS Pathog 2014;10:e1004216.
94. Pal M, Berhanu G, Desalegn C, et al. Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2): An Update. Cureus 2020;12:e7423.
95. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol 2015;1282:1-23.
96. Bartlam M, Yang H, Rao Z. Structural insights into SARS coronavirus proteins. Curr Opin Struct Biol 2005;15:664-72.
97. Weiss SR, Navas-Martin S. Coronavirus pathogenesis and the emerging pathogen severe acute respiratory syndrome coronavirus. Microbiol Mol Biol Rev 2005;69:635-64.
98. Shum KT, Tanner JA. Differential inhibitory activities and stabilisation of DNA aptamers against the SARS coronavirus helicase. Chembiochem 2008;9:3037-45.
99. Jia Z, Yan L, Ren Z, et al. Delicate structural coordination of the Severe Acute Respiratory Syndrome coronavirus Nsp13 upon ATP hydrolysis. Nucleic Acids Res 2019;47:6538-50.
100. Guarner J. Three Emerging Coronaviruses in Two Decades. Am J Clin Pathol 2020;153:420-1.
101. Mirza MU, Froeyen M. Structural elucidation of SARS-CoV-2 vital proteins: Computational methods reveal potential drug candidates against main protease, Nsp12 polymerase and Nsp13 helicase. J Pharm Anal 2020;10:320-8.
102. Panera N, Tozzi AE, Alisi A. The G-Quadruplex/Helicase World as a Potential Antiviral Approach Against COVID-19. Drugs 2020;80:941-6.
103. Seeger C, Mason WS. Molecular biology of hepatitis B virus infection. Virology 2015;479-480:672-86.
104. Rahman MM, McFadden G. Oncolytic Virotherapy with Myxoma Virus. J Clin Med 2020;9:171.
105. Zhang C, He L, Kang K, et al. Screening of cellular proteins that interact with the classical swine fever virus non-structural protein 5A by yeast two-hybrid analysis. J Biosci 2014;39:63-74.
106. Shannon-Lowe C, Rickinson A. The Global Landscape of EBV-Associated Tumors. Front Oncol 2019;9:713.
107. Peng Q, Wang L, Qin Z, et al. Phase Separation of Epstein-Barr Virus EBNA2 and Its Coactivator EBNALP Controls Gene Expression. J Virol 2020;94:e01771-19.
108. Sylvestersen KB, Horn H, Jungmichel S, et al. Proteomic analysis of arginine methylation sites in human cells reveals dynamic regulation during transcriptional arrest. Mol Cell Proteomics 2014;13:2072-88.
109. Chen CJ, Kuo MD, Chien LJ, et al. RNA-protein interactions: involvement of NS3, NS5, and 3' noncoding regions of Japanese encephalitis virus genomic RNA. J Virol 1997;71:3466-73.
110. Jorba N, Juarez S, Torreira E, et al. Analysis of the interaction of influenza virus polymerase complex with human cell factors. Proteomics 2008;8:2077-88.
111. Prasad M, Ranjan K, Brar B, et al. Virus-Host Interactions: New Insights and Advances in Drug Development Against Viral Pathogens. Curr Drug Metab 2017;18:942-70.
112. Shih JW, Lee YH. Human DExD/H RNA helicases: emerging roles in stress survival regulation. Clin Chim Acta 2014;436:45-58.
113. Chan YK, Gack MU. RIG-I-like receptor regulation in virus infection and immunity. Curr Opin Virol 2015;12:7-14.
114. Fiorucci G, Chiantore MV, Mangino G, et al. MicroRNAs in virus-induced tumorigenesis and IFN system. Cytokine Growth Factor Rev 2015;26:183-94.
115. Umbach JL, Cullen BR. The role of RNAi and microRNAs in animal virus replication and antiviral immunity. Genes Dev 2009;23:1151-64.

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