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CRITICAL REVIEW

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Major vault protein plays important roles in viral infection

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Abstract

Viral replication and related protein expression inside the host cells, and host antiviral immune responses can lead to the occurrence of diverse diseases. With the outbreak of viral infection, a large number of newly diagnosed and died patients infected with various viruses are still reported every year. Viral infection has already been one of the major global public health issues and lead to huge economic and social burdens. Studying of viral pathogenesis is a very important way to find methods for prevention, diagnosis, and cure of viral infection; more evidence has confirmed that major vault protein (MVP) is closely associated with viral infection and pathogenesis, and this review is intended to provide a broad relationship between viruses and MVP to stimulate the interest of related researchers.

KEYWORDS

immune response, major vault protein, viral infection

1 | INTRODUCTION

Viruses are acellular that cannot naturally reproduce outside of the living host cells and only assemble themselves depending on the host cellular metabolism.[1] Virion, known as the complete viral particle, consists of nucleic acid surrounded by capsid, which is enveloped with lipids in some viruses. Virion is less than 300 nm in diameter, and its self-assembly is very fast, viral replication inside of the host cells may manipulate and damage the host cells, and the antiviral immune response of the host can damage tissue simultaneously. Under the effort of viral toxicity and host immunity, the host is prone to get many kinds of diseases. Hepatitis B virus (HBV) and hepatitis C virus (HCV) can cause chronic infection, which can lead to liver cirrhosis and subsequently develop hepatocarcinoma, the patients with viral hepatitis serve as reservoirs of infectious virus.[2] Some viruses, including hepatitis A virus (HAV), human enterovirus, Ebola virus, SARS virus, and avian influenza, can cause an outbreak of epidemic infection.[3–6] The typical antibiotics are not effective of antiviral infection, antigenic drift of viruses can make effective treatments ineffective,[7] and treatment of viral infection is still one of challenges for humanity.

Abbreviations: AIDS, acquired immunodeficiency syndrome; ATF, activating transcription factors; C/EBPβ, CCAAT-enhancer-binding protein β; EGF, endothelial growth factor; eIF4A, eukaryotic initiation factor 4A; ERK, extracellular signal-related kinase; IRF7, interferon regulatory factor 7; MAPK, mitogen-activated protein kinase; MDA5, melanoma differentiation-associated protein 5; MDM, monocyte-derived macrophages; MVP, major vault protein; MyD88, myeloid differentiation primary response 88; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; PBMC, peripheral blood mononuclear cells; PKM2, pyruvate kinase isozyme M2; PRRs, pattern recognition receptors; PTEN, phosphatase and tensin homolog deleted on chromosome 10; SRSFs, serine/arginine-rich splicing factors; STAT-1, signal transducer and activator of transcription-1

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Recent studies have shown that many host-encoded proteins are associated with viruses: heat shock protein 70 is incorporated into the virions of human immunodeficiency virus type 1 (HIV-1)[8]; serine/arginine-rich splicing factors (SRSFs) are related to viral replication, SRSF2 promotes anogenital tumorigenesis by maintaining the stability of E6E7 mRNAs of human papillomavirus 16 (HPV16), which is the pathogen of anogenital cancer; HIV-1 replication is increased by SRSF1, SRSF4, and SRSF10 within the host cells[9]; 36 host-encoded proteins are presented in influenza virions[10]; MVP is involved in antiviral immune response[11]; and the study of host-encoded proteins in relation to viruses contributes to finding novel targets for antiviral drugs.

Vaults, the large ribonucleoprotein particles, are composed with MVP, poly (ADP-ribose) polymerase, telomerase-associated protein-1 (TEP1), and one or more noncoding RNA.[12,13] The human MVP, encoded by MVP gene that is located in chromosome 16p11.2,[14] is highly conserved during evolution[15,16] and predominant component of vaults.[17–20] The expression of MVP is very strong and widespread,[21] the MVP is mainly located in the cytoplasm and associated with the cytoskeleton, and a small amount is localized at or around the nuclear membrane and the nuclear pore complex.[22,23] Current studies have confirmed that MVPs are associated with multidrug resistance in treatment of non-small lung cancer,[24] human colon cancer,[25] and mesial temporal lobe epilepsy with hippocampal sclerosis.[26] MVP/Vaults play important roles in several signal transduction pathways, suppress c-Jun-mediated AP-1 transactivation by associating with COP1,[27] participate the phosphoinositide 3-kinase pathway by interacting with endogenous phosphatase and tensin homolog deleted on chromosome 10 (PTEN) with the help of Ca2+ modulation,[28] act as a signaling scaffold protein of extracellular signal-related kinase (ERK)/mitogen-activated protein kinase (MAPK) pathway by interacting with Src in response to endothelial growth factor (EGF),[29] and affect the JAK–STAT signaling pathway by responding and interfering the interferon (IFN)-gamma-mediated STAT1 signals.[30] Growing evidences also confirmed that MVP is closely associated with other multiple cellular processes, such as nuclear–cytoplasmic transport,[31] malignant transformation,[32] senescence/aging,[33] autophagy,[34] and innate immunity.[35] Interestingly, MVP has been linked to several types of viral infectious diseases as well as to virus-mediated immune responses.[29,36] Here, we focus on the roles of MVP in the intracellular viral replication and host immune responses.

2 | MVP PLAYS INHIBITION FUNCTION IN VIRAL REPLICATION BY INDUCING TYPE-1 IFN PRODUCTION

The innate immune response, including the production of IFN-1, is the first barrier of eliminating invaded pathogens early.[37] In host cells, TLRs, RIG-1 (RIG-I-like receptor dsRNA helicase enzyme), and MDA5 (melanoma differentiation-associated protein 5) act as pattern recognition receptors (PRRs), IFN-stimulated proteins, and sensors for viral infection.[38–40] The interferon regulatory factor 7 (IRF7) plays the master transcriptional role in viral infection-induced IFN production and immune responses,[41–43] activates IFN-β production mediated by MyD88 (myeloid differentiation primary response 88)-independent RIG-1/MDA5 pathway, also activates IFN-α production mediated by the MyD88-dependent TLRs pathway.[44–46] The IFN-1 inhibits viral replication (including HCV, influenza A virus [IAV], and HIV) by the production of IFN-stimulated effective proteins.[11,47,48]

After host cells or tissues are infected by HCV, PRRs of host cells recognize stimulation signals of products of HCV processing, the interaction between PRRs and stimulation signals activates IkBa kinase to phosphorylate IkBα,[49] which is associated with NF-kB protein complex in the cytoplasm, phosphorylated IkBα is released from NF-kB complex and degraded by ubiquitin-proteasome pathway,[50] free NF-kB complex translocates to the nucleus, and subsequently activates MVP transcription under coactivators including HCV protein NS5A.[11] HCV infection also induces MVP expression through the SP1 signal pathways, and the infection of vesicular stomatitis virus (VSV), IAV, and enterovirus 71 (EV71) has the same effect with HCV infection.[11] Inducible MVP is helpful for the nuclear translocation of IRF7 and NF-kB, and performs antiviral activity by promoting endogenous IFN-1 production and expression of the IFN-stimulated genes. The production of IFN is the critical step in an innate immune response, and MVP plays strong antiviral activity in an IFN-1-dependent manner.

3 | HBV HBSAG AND HBEAG INHIBIT IFN PRODUCTION INDUCED BY MVP

With the advent of effectively prophylactic vaccines and antiviral drugs, HBV infection remains a global public health problem,[51,52] an estimated 240 million people with chronic HBV infection are HBV carriers,[53] deadly complications of HBV chronic infection (including cirrhosis and

hepatocellular carcinoma) result in approximately 600,000 deaths per year,[54] and HBV infection brings heavy economic pressure for individuals and heavy social burden for the world. As a type of pathogen, HBV causes host cells to produce IFNs to increase protective defense of host immune system,[55] IFNs play important roles of antivirus by regulating the host immune system, and have been used to treat some cancers[56] and HBV infection.[57,58] HBV virus infection leads to the production of Type 1 IFNs by two main pathways. Toll-like receptors 3/4 (TLR 3/4) recognize viral nucleotides and glycolipids and recruit the adaptor protein TRIF (TIR-domain-containing adapter-inducing IFN-β), TRIF interacts with TRAF6 (tumor necrosis factor [TNF] receptor-associated factor 6) to activate NF-kB (nuclear factor kappa-light-chain enhancer of activated B cells), and activated NF-kB provokes IFNb production.[59,60] Another pathway is triggered by TLR7/8 and TLR9, TLRs recognized viral nucleotides in the endosome recruit MyD88,[61] in turn recruit IRAK1/4 (interleukin-1 receptor-associated kinase 1/4)[62] to the complex and interact with TRAF6 (TNF receptor-associated factor 6),[63,64] and then activate IRF5/7 (IFN regulatory factor 5/7) to induce IFNα expression.

MVP is a virus-induced protein, and the level of MVP in peripheral blood mononuclear cells (PBMCs), sera, and liver tissue derived from patients with chronic hepatitis B (CHB) is higher than healthy individuals; MVP expression is also increased in HBV stable expression cell lines (HepG2.2.15 and HuH7.37) and HBV-infected hepatocarcinoma cell lines (HepG2 and HuH7).[11] During HBV infection, TLRs recruit and activate MyD88, which interacts with IRAK1/4, IRF5/7, and TRAF6 to form a complex,[62] the middle domain (aa 310–620) of MVP can interact with MyD88, high expressed MVP joins the MyD88-mediated complex by interacting with MyD88 to promote IFN-1 production through translocation of IRF7 and NF-kB from the cytoplasm to the nucleus.[11,65] However, HBsAg and HBeAg competitively bind the MyD88-binding region of MVP and suppress the IFN-1 production by disrupting MVP/MyD88 interaction; the IFN-1 increment effect induced by MVP is counterattacked through HBeAg and HBsAg binding to MVP[11] (Figure 1). Evidence suggests that HBV has other strategies to suppress the host immune response. HBV polymerase (Pol) may inhibit IFN-α-induced MyD88 induction,[66] HBeAg suppresses TLR-induced IFN-β,[67] HBsAg can block the IRF-7 mediated IFN-α production pathway,[68] and multiple mechanisms lead to HBV immune escape.

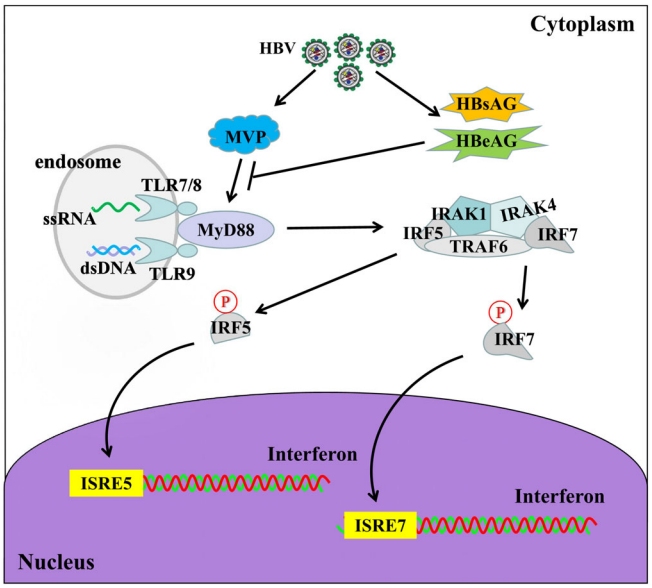

FIGURE 1 HBsAg and HBeAg weaken the effect of MVP on promoting IFN production

4 | MVP PLAYS A PIVOTAL ROLE IN PROINFLAMMATORY RESPONSE CAUSED BY VIRAL INFECTION

When the host is attacked by harmful pathogens including viral infection, one of protective immune response is inflammation to eliminate damage.[69] IFN to interfere viral replication,[55] interleukin 6 (IL-6) acted as a pro-inflammatory cytokine,[70] and interleukin 8 (IL-8) served as a chemokine for neutrophils and monocytes[71] are important mediators of immune response, and activation of IL-6 and IL-8 gene expression is regulated by transcription factors.[72,73] Activator protein 1 (AP-1), composed of proteins belonging to c-Fos, c-Jun, activating transcription factors (ATF) and Maf families,[74] is a heterodimeric complex and acts as a transcription factor.[75] The function of AP-1 complex is heavily dependent on the c-Fos and c-Jun subunits,[76] AP-1 complex binds DNA at AP-1 specific sites at the promoter and enhancer regions of target genes and increases target gene expression,[77,78] and researchers had confirmed that the AP-1 complex is involved in IL-6 and IL-8 regulation.[79,80] CCAAT-enhancer-binding protein β (C/EBPβ) is a member of the C/EBP transcription factor family, the gene of C/EBPβ can be translated into three polypeptides: the 38 kDa and 34 kDa liver-enriched transcriptional activating proteins (LAPs), and the 20-kDa liver-enriched transcriptional inhibitory protein (LIP).[81] C/EBP proteins interact with certain gene promoters containing CCAAT box motif, then recruit co-activators to promote gene expression.[81] The promoters of IL-6 and IL-8 consists of the CCAAT box motif region, wherein C/EBPβ can bind and affect IL-6 and IL-8 expression.[82]

In order to restrict the spread of infected virus, some activated transcription factors contribute to the production of inflammatory-related cytokines and chemokines. IAV, as a kind of negative single-stranded RNA viruses (ssRNA), produces replicative intermediate double-stranded RNA (dsRNA) in the infected cells,[83] dsRNA and the synthetic dsRNA analog polyinosinic–polycytidylic acid (poly[I:C]) are recognized by TLR3,[29,84] then activate the TLR3-IFN production pathway to robustly express type I IFNs.[59,60] MVP, as a regulator in the proinflammatory response and an effector in IFN signaling pathway, increases to against viral replication during viral infection.[65] MVP has been proven to be a nuclear–cytoplasmic transport protein[30] and interacts with c-Fos of the AP-1 complex components and C/EBPβ-LAPs.[48] The interaction promotes the AP-1 complex and C/EBPβ-LAPs translocation from the cytoplasm to nucleus and follows to activate the IL-6 and IL-8 expression by the AP-1 complex and C/EBPβ-LAPs binding to the IL6 and IL8 promoters, and MVP plays a synergistic role in the expression of IL-6 and IL-8.[48] The expression of MVP, IL-6, and IL-8 increases simultaneously in IAV-infected A549 or dsRNA-stimulated PBMCs, and the expression of IL-6 and IL-8 is impaired in MVP knockdown cells and knockout mice[48]; MVP plays a pivotal role in virus-triggered proinflammatory response by mediating the AP-1 and C/EBPβ signaling pathways. The model of MVP functions for proinflammatory response is summarized in Figure 2.

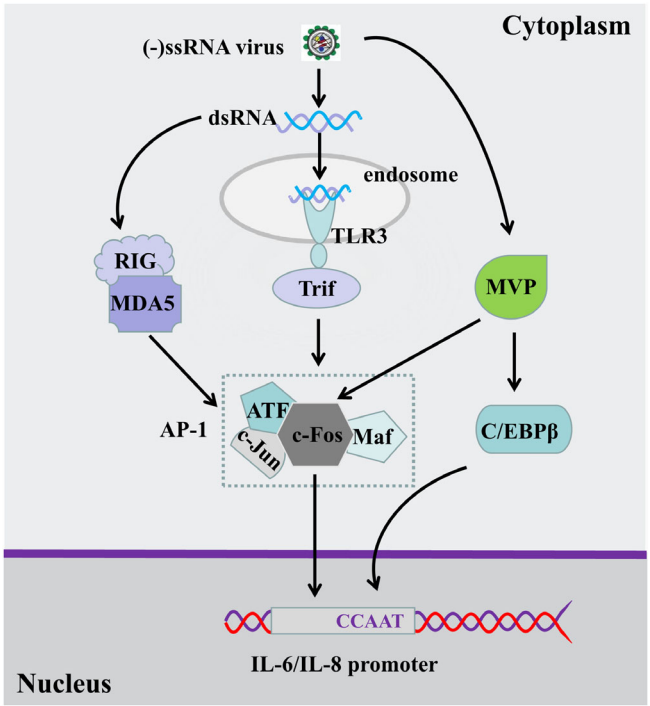

FIGURE 2 MVP plays a pivotal role in the proinflammatory response caused by (−) ssRNA viral infection

5 | MVP PLAYS OPPOSITE ROLES ON ANTI-HEV INFECTION AND TREATMENT WITH SILVERTROL FOR HEV INFECTION

Hepatitis E virus (HEV), belonged to the genus *Hepevirus*, is classified as a positive-strand RNA virus ([+] ssRNA virus),[85] and HEV infection is an important public health problem. HEV is mostly transmitted via the fecal–oral route in developing countries under poor sanitary conditions,[86,87] and often spread in many countries by food borne,[88] blood transfusion,[89,90] and zoonotic origin.[91] HEV can cause chronic infection in immunosuppressed patients, pegylated IFN-alpha-2b is used in the treatments for chronic hepatitis E (CHE) virus infection in liver transplant patients,[92] pegylated IFN-alpha-2a is used in the treatments for CHE virus infection in a hemodialysis patient,[93] and ribavirin as monotherapy may be effective in the treatment for CHE virus infection in solid-organ transplant patients.[94]

Silvestrol is a natural cyclopenta(b)benzofuran and acts as an inhibitor of the eukaryotic initiation factor 4A (eIF4A) via hindering translation initiation from the 5′-capped and 5′-UTR of mRNAs.[95] The HEV is a (+) ssRNA virus containing 5′-cap and 5′-UTR structure,[96] the released HEV particles from persistently HEV-infected A549 cells treated with silvestrol are robustly reduced, which are caused by the decrease of the intracellular HEV capsid protein.[97] Silvestrol also affect the expression and localization of antiviral host factor MVP, the MVP amount of the cytoplasm is reduced after treating with silvestrol in HEV-infected cells, and the MVP transfers from the cytoplasm to the perinuclear area[97] that affects MVP-mediated IFN production.[98] The translation of MVP is highly activated to play an antiviral role by HEV infection; however, the change of translation and cytoplasmic localization affected by the silvestrol treatment counteracts part of antiviral effect, MVP plays a complex interplay between the anti-HEV replication and the effect of treating with silvestrol for HEV infection.

6 | MVP IS ASSOCIATED WITH HIV REPLICATION BY PARTICIPATING CYSTATIN B-MEDIATED INHIBITION OF INF RESPONSE

The infection of HIV is the pathogenesis of acquired immunodeficiency syndrome (AIDS) and one of major global public health issues.[99] HIV infected immune cells, including monocytes, lymphocytes, and macrophages, act as stable rival reservoirs,[100] and are main barrier to

eradicate virus by antiviral therapy.[101] The level of cystatin B, a cysteine protease inhibitor, is higher in blood monocyte-derived macrophages (MDM) than in placental macrophages, which are more resistant to HIV-1 infection than MDM.[102,103] The expression of cystatin B is upregulated in HIV-1-infected MDM,[104] and cystatin B promotes HIV-1 replication by interacting with pyruvate kinase isozyme M2 (PKM2),[105] which is associated with the cocaine enhancement of HIV-1 replication.[106] In HIV-infected MDM, upregulated cystatin B interacts with MVP[105] and signal transducer and activator of transcription-1 (STAT-1).[103] MVP, as an IFN-responsive protein, directly inhibits tyrosine phosphorylation of STAT-1 to weaken IFN-induced antiviral response by interfering the JAK/STAT signal pathway,[29] then promote HIV replication. Cystatin B directly interacts and decreases tyrosine phosphorylation of STAT-1, and inhibits IFN-β response and STAT-1 translocation from the cytoplasm to nucleus to reduce JAK/STAT signal pathway activity, and ultimately promote HIV replication.[105] Under the cooperation of the cystatin B and MVP, HIV replication is activated by the damage of JAK/STAT signal pathway activity mediated by the low tyrosine phosphorylation of STAT-1.

7 | CONCLUSIONS AND PERSPECTIVES

MVP is involved in the diversely cellular processes, including multiresistant cancers,[24–26] signal transmission pathways,[27–30] and immune response associated with viral infection and treatment.[11,48,65,97,105] Viruses with divergent virulence and spreadways can cause diverse human diseases with different types and degrees of damage, as a response of viral infection, studies have confirmed that MVP is enhanced in diverse viral infection, including HBV, HCV, HIV, IAV and VSV, and so on. The infection of (−) ssRNA viruses (including HCV, VSV, IAV, and EV71) or dsRNA stimulation activates proinflammatory response by inducing the expression of MVP, IL-6, and IL-8, enhanced MVP further increase the expression of IL-6 and IL-8 by translocating transregulatory elements (AP-1 protein complex and C/EBPβ-LAPs) to the nucleus,[65] and lipopolysaccharide synthesized during viral replication also activates the TLR4 signaling pathway to induce cytokines, chemokines, and IFN-1 against IAV replication[107]; however, the value of MVP in the diagnosis, treatment, and prognosis of viral infection remains unclear and additional studies are still required. HBsAg and HBeAg compete to bind with MVP, facilitate HBV replication and survival by attenuating the effect of MVP-induced IFN,[48] and IFN and nucleotide analogs (NAs) are used for the treatment of patients infected with HBV, the stage of liver diseases is important in guiding antiviral therapy[108]; however, the effect of MVP on the severity of liver disease and the efficacy of different treatments is unclear. Silvestrol, as a potent antiviral compound, inhibits HEV assembly by interfering HEV capsid protein translation, but deactivates the antiviral effect of MVP by translocating MVP to the perinuclear membrane[97]; cystatin B, as a cysteine protease inhibitor, increases HIV replication by interacting with MVP and PKM2 to inhibit IFN response and tyrosine phosphorylation of STAT-1.[105] MVP plays an opposite role in HIV infection by comparing with IVA and HBV infection, weakens the antiviral efficacy of silvestrol in the treatment of HEV infection, and additional studies are necessary to clarify the role of MVP more clearly in viral infection.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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