

Review

The Interplay of Viral and Host Factors in Chikungunya Virus Infection: Targets for Antiviral Strategies

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Abstract: Chikungunya virus (CHIKV) has re-emerged as one of the many medically important arboviruses that have spread rampantly across the world in the past decade. Infected patients come down with acute fever and rashes, and a portion of them suffer from both acute and chronic arthralgia. Currently, there are no targeted therapeutics against this debilitating virus. One approach to develop potential therapeutics is by understanding the viral-host interactions. However, to date, there has been limited research undertaken in this area. In this review, we attempt to briefly describe and update the functions of the different CHIKV proteins and their respective interacting host partners. In addition, we also survey the literature for other reported host factors and pathways involved during CHIKV infection. There is a pressing need for an in-depth understanding of the interaction between the host environment and CHIKV in order to generate potential therapeutics.

Keywords: chikungunya virus; host factors; potential therapeutics; interactions; antiviral; viral structural proteins; viral non-structural proteins

1. Introduction

In recent years, chikungunya virus (CHIKV) has re-emerged as one of the many arthropod-borne viruses (arboviruses) that can pose serious international public health threats [1,2]. CHIKV is an Alphavirus that belongs to the *Togaviridae* family and is transmitted mainly by two species of mosquitoes, namely, *Aedes albopictus* and *Aedes aegypti* [3]. Chikungunya comes from a Makonde word that refers to the bent-up posture that the disease induces [4]. CHIKV can be classified into three different lineages with distinct genotypes corresponding to their respective geographical origins. They include the Asian, East-Central-South African, and West African genotypes [5–8]. One unique feature, which distinguishes CHIKV from its arguably well-conserved alphavirus cousins, is its high serum viral loads, which can exceed 10^9 virus particles/mL [9]. This remarkable feature allows easy transmission of the CHIKV to any feeding mosquitos.

According to historical records, CHIKV is likely to have been present since 1779 [10]. However, due to the similar clinical manifestations between CHIKV and dengue infections, CHIKV-infected patients were likely to have been initially misdiagnosed as having dengue infection [10,11]. CHIKV was first isolated and identified during an outbreak in Tanzania in 1953 [4]. Thereafter, many epidemics and outbreaks were documented in a number of African countries in 1958 with thousands of people being infected [12]. Soon after, cases of CHIKV infection mushroomed in many Southeast Asian countries from the 1960s [13]. Between 2005 and 2006, a major unprecedented epidemic of CHIKV swept across many countries within the Indian Ocean territories, where CHIKV was not endemic [13].

During that outbreak, one-third of the 785,000 residents of La Réunion were infected with CHIKV, with a 0.1% fatality rate [14,15]. This ever-expanding geographical range of CHIKV infection seemed unstoppable [16,17]. In 2007, autochthonous CHIKV cases were reported in Italy, making the first instance of an outbreak in temperate regions [18]. Outbreaks and other autochthonous transmission events were subsequently reported in many non-endemic regions like Singapore from 2006 to 2015; France (West-French indies, Caribbean islands) from 2013 to 2015; Spain and Senegal from 2014 to 2015; Argentina, The United States of America, and Kenya in 2016; and Italy in 2010, 2014, and 2017 [19–24].

CHIKV-infected patients experience a sudden onset of fever of about 40 °C, together with the trademark symptoms of intense muscle pain in the arms, calves, and thighs, as well as arthralgia in the ankles, elbows, knees, and wrists within 2 to 12 days of infection [25]. This is due to CHIKV's ability to infect both the skeletal muscle progenitor cells and fibroblasts in the connective tissues of muscles and joints, where a high density of nociceptive nerve endings reside [26–28]. In addition, patients also suffer from maculopapular rash, nausea, vomiting, headaches, lymphopenia, and moderate thrombocytopenia [29,30]. The more severe cases, though rare, involve the manifestation of neurological complications. In addition, there are a few cases of CHIKV causing miscarriages and neonatal complications like neonatal encephalopathy after maternal-to-fetal transmission [31–34]. The immunopathogenesis of CHIKV infection has been extensively reviewed by Burt and colleagues [35].

These acute symptoms usually resolve within two weeks. However, a significant portion of patients experience persistent and/or recurrent joint pains for months or years after contracting CHIKV [36,37]. The mechanism of the progression of the CHIKV disease to the chronic phase remains poorly characterized. However, recent studies have shown that macrophages may play a role in the chronic manifestations of CHIKV [38,39].

Despite the significant healthcare threat posed by the CHIKV, there are still no available vaccines or therapeutics for CHIKV infections [1,35]. Patients are usually given analgesics and anti-inflammatory drugs to relieve symptoms. Even though there are a number of anti-CHIKV compounds being reported, precise mechanistic data of these compounds, as well as efficacy studies in mouse models, are lacking. Ribavirin and chloroquine are the only two drugs that have been tested in clinical trials [40]. Despite having promising *in vitro* data, chloroquine was found to be ineffective in clinical trials [41,42]. On the other hand, Ribavirin was found to be effective in alleviating chronic symptoms. However, the clinical trial cohort (20 patients) was too small to provide conclusive evidence [43]. Therefore, there is a pressing need to identify and develop novel antivirals to combat CHIKV infection.

Although attempts to develop drugs that specifically target viral proteins have proven to be successful, the process is rather time-consuming and costly [44–48]. Furthermore, these compounds were found to often display narrow spectrum activities [49]. One promising approach is to target host factors that are known to be hijacked by viruses using either new compounds or to repurpose existing approved drugs [50–52]. However, there are still many gaps in the current knowledge of basic virology and replication of CHIKV, which poses difficulties for the discovery of anti-CHIKV therapeutics. The purpose of this review is to provide an overview of the existing research thus far on the interplay of viral and host factors during CHIKV infection. We hope this will guide further research into potential druggable targets in the discovery of potential therapeutics.

2. CHIKV and Its Replication Cycle

CHIKV is an enveloped, spherical virus with a diameter of about 60–70 nm [53–55]. The CHIKV genome consists of a single-stranded, positive-sense, linear RNA that is about 11,800 nucleotides long [56,57]. The 5' end of the positive-sense RNA genome possesses a 7-methylguanosine cap, and the 3' end has a polyadenylated tail [58]. There are two open reading frames (ORF) found in the CHIKV genome, one for the non-structural proteins, the other for the structural proteins. The first ORF encoding the non-structural proteins (nsP1, 2, 3, and 4) makes up nearly two-thirds of the genome [56]. The remaining one-third portion encodes for the five structural proteins (capsid, E3, E2,

6K, and E1) [56]. The CHIKV genome contains three non-translated regions (NTR) [56,58]. The 5' NTR consists of 76 nucleotides, while the 3' NTR is composed of 526 nucleotides [59]. The remaining NTR, which is 68 nucleotides long, is found between the two ORF and carries a promoter sequence that allows the generation of the 26S subgenomic RNA that encodes all the structural proteins [59]. The CHIKV genome is enclosed within the nucleocapsid core in the mature virion. The nucleocapsid, made up of 240 units of capsid proteins [56], is in turn surrounded by an envelope made up of a host-derived lipid bilayer. The CHIKV envelope is studded with 80 sets of trimeric spikes, with each spike containing three E1-E2 heterodimers, which mediate entry into host cells [60,61].

Upon binding to the host cell receptor via E2 protein, the CHIKV particle is endocytosed by the host cell via the clathrin-mediated pathway in a process involving Eps15 (epidermal growth factor receptor pathway substrate 15), although clathrin-independent entry has also been reported [62–66]. Within the early acidic endosome, the low pH environment initiates the fusion of the viral envelope and the endosomal membrane in a process mediated by the E1 protein [63,65–68]. The membrane fusion process occurs rapidly (within 40 s after endocytosed) in Ras-related protein 5 (Rab5)-positive endosomes and is found to be highly dependent on the presence of cholesterol [66]. Thereafter, the virus disassembles releasing the viral RNA genome into the cytosol [68,69]. By hijacking the host translational machinery, the first two-thirds of the viral RNA is rapidly translated into a polyprotein (P1234), which consists of all the four non-structural proteins [53,56]. However, this polyprotein (P1234) makes up to only 10% of all the translated transcripts due to the presence of an opal stop codon between the nsP3 and nsP4 gene [58]. The remaining 90% is made up of the P123 polyprotein. The opal stop codon is believed to play a role in regulating the levels of the nsP4 by the alphaviruses [70]. P1234 is subsequently cleaved in *cis* by the viral protease nsP2 yielding P123 and nsP4 [53]. This allows the formation of an initial but unstable replication complex, which allows the synthesis of negative-sense strand viral RNA. At this phase of the replication cycle, structures known as spherules, which are derived from the plasma membranes, can be observed to be studded along the plasma membrane. The unstable P123-nsP4 complexes are proposed to be localized near the neck of these spherules, which functions in protecting the double stranded RNA intermediates from detection and degradation [71–73].

As the infection progresses, the spherules become internalized and contribute to the formation of a membranous structure called virus-induced type 1 cytopathic vacuoles (CPV-I) [72–74]. A recent study by Thaa and colleagues showed that most of the spherules induced by CHIKV infection remain at the plasma membrane, and that the internalization of the spherules is dependent upon the activation of the phosphatidylinositol-3-kinase-Akt-mTOR pathway [75]. The CPV is a typical membranous structure (derived from both endosomes and lysosomes) found in *Alphavirus*-infected cells that allows active synthesis of both the negative-sense RNA intermediate and the positive-sense viral RNA [72–74]. The accumulation of the P123-nsP4 complexes eventually crosses a certain stoichiometric threshold concentration leading to the cleavage of P123 in *trans*, releasing nsP1 protein [76,77]. This results in a more stable replication complex within CPV-I, made up of nsP1, P23, and nsP4 [78–80]. A stable replication complex is subsequently formed upon the final cleavage of P23 into nsP2 and nsP3 proteins. This induces a switch from the synthesis of the negative-sense RNA intermediate to the synthesis of both the full-length viral genome and the 26S subgenomic RNA [74,81].

The 26S subgenomic RNA (which encodes only the structural proteins) is then translated into structural polyproteins [56]. Once the full length capsid protein has been translated, it undergoes autocleavage almost immediately, while the translation of the remaining structural proteins continues [57,82–84]. In addition, upon its self-cleavage, the capsid protein is able to recognize the full-length genomic viral RNA [82–84]. The capsid proteins then oligomerize, packaging the viral genome into the nucleocapsid core [85,86]. Again, similar to the non-structural proteins, two types of structural polyprotein products can be identified after the self-cleavage of the capsid protein. The presence of the major structural polyprotein (consisting of E3, E2, 6K, and E1) and the minor one (10–18%) (containing only E3, E2, and TF) have been attributed to the slippery codon

motif (UUUUUUA) found on the 6k gene, resulting in a -1 ribosomal frameshifting event [87,88]. These structural polyproteins are then directed by the signal peptide found on the N-terminus of the E3 protein to the endoplasmic reticulum membrane, where they undergo complete cleavage into individual proteins (pE2 (E3-E2), 6K or TF, and E1) by host proteases [89]. E1 and pE2 proteins associate noncovalently, forming a heterodimer complex, which undergoes posttranslational modifications as it gets shuttled via the Golgi secretory pathway. The host furin cleaves pE2, resulting in a mature E2 viral protein [90–94]. Soon after, fully developed nucleocapsid cores carrying full-length, positive sense genomes are recruited to the cell plasma membrane where they bud out of the host cells, simultaneously acquiring a portion of the host plasma membrane studded with mature envelope glycoproteins, making up the envelope of the mature virion [53].

It is also interesting to note that in the late phase of infection, another type of cytopathic vacuole called CPV-II can be observed in infected cells [95–97]. In contrast to CPV-I, CPV-II originate from the trans-Golgi network [98,99]. Within these vacuoles, the viral envelope glycoproteins (E1 and E2) have been found to be arranged in a hexagonal lattice and packed in arrays of helical tube-like structures [98,100]. In addition, nucleocapsids have also been observed along the periphery of the cytoplasmic side of CPV-II [96,98,100]. Given that these structures are in close proximity to the plasma membrane, it is postulated that they aid in viral assembly and/or transport of the envelope proteins to the plasma membrane and viral release via a second mechanism, exocytosis [98,101].

3. Interplay of Host Factors with CHIKV Structural Proteins

Structural proteins are known to be involved in processes like entry, fusion, uncoating of virus particle, assembly of virions, and budding. Here, we present a brief review of the functions of each individual viral proteins and their reported interacting host factors.

3.1. Capsid Protein

The CHIKV capsid protein is a compact multifunctional protein of 261 amino acids with a molecular weight of about 30 kDa [58,102,103]. Unlike the New World encephalitic alphaviruses, the capsid proteins of CHIKV (an Old World arthritogenic alphavirus) do not seem to be involved in the shutting down of the host transcriptional processes [104]. Instead, the Old World arthritogenic viruses rely on nsP2 for inducing host transcriptional and translational shutoff [104].

The capsid protein is made up of three main regions (regions 1, 2, and 3) [105,106]. Region 1 (1–80 aa) being highly basic in nature (Arg-, Lys-, and Pro-rich), is proposed to be able to bind RNA in a non-specific manner and may also be involved in protein interactions that inhibit host transcription [106]. In contrast, region 2 (81–113 aa) binds specifically to the full length viral RNA genome and also plays an important role in the oligomerisation of other capsid proteins in order to form mature nucleocapsid particles [85,106–109]. Region 3 is a serine protease containing a conserved catalytic triad (His 139, Asp 161, and Ser 213) that is able to cleave itself in *cis* and inactivate itself by binding its active site with its C-terminal tryptophan residue [53,82,83,110]. A recent study reported that the CHIKV capsid is also able to exhibit *trans*-cleavage properties [111]. In addition, the hydrophobic pocket (containing interacting residues: Val 130, Gly 131, Val 134, Met 135, Trp 245, and Val 250) located on region 3 was found to interact with Pro 404 of the E2 cytoplasmic domain, which is believed to occur during mature particle assembly [102,106,112]. Moreover, dimerization of two capsid protein monomers relies on the interaction of the Tyr 186 residue from one monomer with two Asn residues at positions 188 and 220 from the other monomer, all of which are located on region 3 [102].

The CHIKV capsid protein has been reported to possess both one nuclear import (NLS) and two nuclear export signals (NES) (44–53 aa & 143–155 aa), which allows the protein to traverse actively between the nucleus and cytoplasm [113,114]. In addition, two host proteins, karyopherin α (Kara α) and chromosomal maintenance 1 (CRM1), have been found to be involved in the active nuclear import and export of the CHIKV capsid protein, respectively [113]. Interestingly, both NES are required to

be intact for CHIKV capsid to be exported. Mutation of the NES near the N-terminus (44–53 aa), by replacing the Lys 51 and Met 53 with alanines, resulted in the retention of the CHIKV capsid within the nucleus [114]. Unexpectedly, this led to the blockage of the host nuclear import system through a mechanism which remains unknown [114]. In addition, Taylor and colleagues showed that mutating the nucleolar localization sequence (NoLs) within the N-terminus results in an attenuated phenotype with smaller plaques and reduced virulence in mice while still being able to elicit an immune response [113–115]. The precise location of the NLS of the CHIKV capsid has yet to be confirmed. Jacobs and colleagues suggested that the location falls between 1 and 83 aa of the capsid protein, whereas Thomas and colleagues reported that it should be between 60 and 99 aa.

Given that the capsid protein is such a crucial, multifunctional viral protein with such an array of functions, more efforts could be channeled to uncover the possible interactions with other potential host factors.

3.2. E3 Protein

E3 proteins carry a signal peptide (a series of polar residues) at their N-terminus, which is crucial for targeting the structural polyprotein towards the endoplasmic reticulum for initial processing [53,106]. Despite being only 64 amino acids long (~7.4 kDa), it is necessary for the stabilization and maturation of the E2 glycoprotein [58,87,116,117]. From crystal structures, the E3 protein was observed to bind exclusively to the E2 protein [118]. It requires the host furin enzyme to mediate the maturation of the E2 protein by cleaving it in the trans-Golgi system only after dimerization with other available E1 glycoproteins is complete [106,118]. After cleavage, the E3 protein continues to associate non-covalently with the E1-E2 spikes by relying on the interaction between the Tyr 47 residue on E3 and the Tyr 48 on the E2 [119]. It is not incorporated into the virus and will dissociate when the entire complex is exposed to neutral pH at the plasma membrane surface [119]. Upon dissociation, the acid-sensitive region between the E2 and E1 glycoproteins gets exposed, priming the E1 protein for activation upon contact with low pH during entry [106,119]. E3 therefore plays an important role in protecting the envelope glycoproteins from low pH and preventing their premature activation. No other host factors that interact with the E3 protein have been reported.

3.3. E2 Protein

The E2 protein (423 aa, ~40 kDa), a type I transmembrane glycoprotein, has long been known to be the main antigenic and receptor binding protein for CHIKV [58,120]. The CHIKV exhibits a wide tropism by being able to replicate in many invertebrate and vertebrate cells [27,65,121–123]. In addition, E2 proteins also serve as stabilizing factors (together with E3 proteins) for the E1-E2 heterodimer during the entire intracellular transport through the secretory pathway, where folding and post-translational modifications take place, and finally to the plasma membrane [106].

To date, no bona fide receptor has been identified for CHIKV. However, there are host factors that have been reported to aid in viral entry. For instance, prohibitin (PHB) was identified to aid in the binding of CHIKV to CHME-5 microglial cells [124]. Wintachai and colleagues also suggested that the possibility of additional co factors that assist the CHIKV entry as poor infection was observed in U937 monocytic cells that also express PHB [124]. In a follow up study, Wintachai and colleagues showed that flavaglines (prohibitin ligand) was able to inhibit CHIKV entry by preventing the CHIKV and prohibitin from colocalising in HEK293T/17 cells [125,126]. These studies suggest that PHB may be the putative receptor for CHIKV. In addition, ATP synthase β subunit was found to be involved in the entry of CHIKV into *Aedes aegypti* mosquito cell lines [127]. Additional host factors like protein tyrosine phosphatase non-receptor type 2 (PTPN2), fibril-forming collagen (COL1A2), and actin gamma 1 (ACTG1) were also shown to interact with the E2 proteins in immunoprecipitation experiments [128]. However, further mechanistic studies are required to understand the role of these proteins during CHIKV infection.

Jemielity and colleagues showed that overexpression of either human T-cell immunoglobulin and mucin-domain containing proteins 1 (hTIM1) or AXL receptor tyrosine kinase (also known as UFO) of the TAM family of kinases promoted entry of CHIKV by at least 8-fold in HEK293T cells [129]. Their work also showed that CHIKV entry is phosphatidylserine (PS)-dependent, as the PS binding deficient hTIM1 variant did not support viral entry [129]. This suggests that PS is exposed on the membrane of the CHIKV, similar to other enveloped viruses, including Pichinde virus, vesicular stomatitis virus, and vaccinia virus [130,131]. By taking advantage of the exposed PS, the CHIKV is able to enter the cells. However, the authors noted that the blocking of hTIM1 receptors was less effective in preventing CHIKV entry in Huh7 cells [129]. In addition, there are no reported interactions between hTIM1 and the CHIKV receptor-binding protein, E2. This suggests that the PS-recognising TIM and TAM receptors may not be the bona fide receptors for CHIKV but instead may play a role as attachment factors that enhance CHIKV infectivity.

Recent work has shown that only the two surface-exposed domains (domains A and B) of CHIKV E2 are able to bind to cells [132]. Binding of the CHIKV with soluble GAGs was found to be able to inhibit CHIKV infection by up to 90% [132]. In addition, only domain A was able to bind to cell-surface glycosaminoglycans (GAGs)-deficient cells, while domain B was found to interact exclusively with cells expressing GAGs on their cell surface [132]. These results suggest that CHIKV could employ more than one entry mechanism, which most probably explains the wide tropism of cells observed. Therefore, more efforts could be directed to uncover other host factors/potential receptors that could interact with the CHIKV E2 proteins.

3.4. 6K/TF Protein

The TF (~8.3 kDa) protein possess the same N terminus as 6 K (61 amino acids ~6.6 kDa) but differs by having a longer basic C terminus (~15 residues) instead of a shorter, hydrophobic C terminus found on 6 K [58,87,88]. Unlike other structural proteins, the exact functions of both 6K and TF have not been clearly elucidated [133]. However, studies on other alphaviruses have suggested that these viral accessory proteins mediate membrane permeability and viral budding, and may also be involved in forming ion channels [87,134,135]. In addition, both 6 K and TF are also incorporated in low levels into mature virions and are crucial in preserving both the stability and infectivity of the virus [136–138]. However, no host factor has been found to interact with either of these proteins.

3.5. E1 Protein

The E1 protein (435 amino acids, ~44 kDa), a class II viral fusion protein, mediates the fusion of the viral envelope with the host endosomal membrane after endocytosis [58,120,139]. This results in the release of the nucleocapsid into the cytoplasm. A single mutation of Ala 226 to a valine residue on the E1 glycoprotein enhanced the dissemination of CHIKV into the secondary organs of *Aedes albopictus* mosquitos. Moreover, this phenomenon was also detected in the suckling mice [140]. This mutation coincided with the emergence of *Aedes albopictus* as a second transmission vector during the Indian Ocean epidemic in 2004 [15]. Moreover, in a recent study by Hoornweg and colleagues, this mutation reinforced the cholesterol-dependent membrane fusion of the CHIKV with the host endosomal membranes [66]. In another recent paper, another two epistatic mutations (E1:K211E together with E2:V264A) were also found to notably enhance transmission (62 fold), infection (13 fold), and dissemination (15 fold) in *Aedes aegypti* mosquitos [141]. However, the exact mechanisms and possible interacting host factors that may facilitate the enhanced fitness of the virus are still unknown.

In an attempt to uncover host proteins that interact with E1, Dudha and colleagues performed a yeast two-hybrid (Y2H) screening on a human brain cDNA library [128]. The screen was able to identify 5 interacting host proteins (copper metabolism (Murr1) domain containing 1 (COMMD1), thrombospondin 1 (THBS1), dynein, cytoplasmic 1, heavy chain 1 (DYNC1H1), ATPase Na⁺/K⁺ transporting beta 3 polypeptide (ATP1B3), and microtubule-associated protein 1B (MAP1B)).

Of these, four hits (COMMD1, THBS1, DYNC1H1, and ATP1B3) passed and were validated via immunoprecipitation and ELISA [128]. However, the biological significance and exact mechanisms of the interactions have yet to be explored.

A second study reported that bone marrow stromal antigen 2 (BST-2 or tetherin or CD317) was able to restrict and trap CHIKV on the surface of the host plasma membrane by engaging the E1 glycoprotein [142]. BST-2 knockout mice suggest that BST-2 is able to protect the lymphoid tissues and regulate the inflammatory response induced by the CHIKV. Moreover, another study showed that the longer isoform of BST-2 was found to specifically block the exit of alphaviruses (e.g., SFV and CHIKV) efficiently [143]. In addition, although rubella virus and dengue virus share similar virion structure as the alphaviruses, they responded differently to the presence of BST-2, with the dengue virus not getting inhibited at all [143].

All in all, though much efforts have been focused on uncovering potential interacting host factors, there are still many gaps in our knowledge understanding the interaction of the host factors with the CHIKV structural proteins.

4. Interplay of Host Factors with CHIKV Non-Structural Proteins and Functions

The major function of CHIKV non-structural proteins (nsPs) is to replicate the viral genome for translation of structural proteins and for packaging into progeny virions. Aside from this, most nsPs also have additional functions outside of the replication complex. Here, we will present a brief review of the functions of each individual viral protein and their reported interacting non-immunological host factors.

4.1. Nonstructural Protein 1 (nsP1)

The nsP1 (535 amino acids, ~60 kDa) protein is responsible for the capping of both the positive-sense genomic viral RNA and the 26S subgenomic RNA [58,144]. Interestingly, it caps the viral RNA in a non-canonical manner where it first attaches a methyl group (hijacked from the host S-adenosyl-methionine (AdoMet)) to a GTP before transferring the methylated guanylate residue to the nsP2-processed 5' end of the viral RNA [145,146]. For the capping to be successful, the triphosphates on the 5' end of the viral RNA need to be cleaved by the nsP2 triphosphatase, exposing the diphosphates to allow the transfer to be complete [145]. Capping of the CHIKV RNA is believed to be a strategy to confer protection against degradation by the host exonucleases and also enable efficient translation of the viral mRNA.

To date, there is still no high resolution structural information on the nsP1 protein [147]. However, it has been suggested that the capping domain spans across at least the first 400 aa residues from the N terminus [148]. With reference to the secondary structure of the nsP1 of Sindbis virus (SINV), a related alphavirus, the CHIKV nsP1, has been speculated to carry guanylyltransferase activities [149]. However, it is important to note that the sequence (or structural) homology between SINV and CHIKV nsP1 is low, and a crystal structure and further confirmatory biochemical assays would be needed for confirmation of the guanylyltransferase activity of CHIKV nsP1. Another important function of the nsP1 protein is its monotopic interaction with the cytoplasmic side of the plasma membrane bilayer, mediated by its amphipathic alpha helix (approximately between 244 and 263 aa), discovered in a relatively well-studied, close alphavirus relative, the Semliki Forest virus [150,151]. Additionally, covalent palmitoylation of the nsP1 (417–419 aa) was discovered to be able to strengthen the association with the plasma membrane [149]. This crucial interaction allows the nsP1 to direct and anchor the replication complex to the cell plasma membrane [152]. The interactions between the nsPs have not been well explored. However, there are studies that have shown that nsP1 strongly interacts with nsP4 [153–155]. Similarly, there is also a lack of studies on the interaction with host proteins. The BST-2 protein was identified to be an anti-viral factor that was downregulated by the nsP1 protein to allow release of the viral particles tethered to the cell surface [142,143,156].

4.2. Nonstructural Protein 2 (nsP2)

The nsP2 protein is one of the more well-studied and also the largest nsP, consisting of 798 amino acids with an approximate molecular weight of 90 kDa [58,144]. So far, there are no reports of high resolution crystal structures of the entire CHIKV nsP2. However, crystal structures of the CHIKV nsP2 C terminus (~471–791 aa) (PDB code 3TRK (2011) and 4ZTB (2016)) and that of alphavirus relatives, SINV, and Venezuelan equine encephalitis virus (VEEV) are available for comparison [157–159]. The domains in the N terminal region, however, have been proposed via molecular modelling [160]. Starting from the N terminus, the nsP2 is hypothesized to have three structural domains [160]. The first domain (~1–167 aa) has little homology with other alphaviruses and remains unknown [160]. The subsequent two domains (~168–470 aa) possess characteristic RecA-like domains of superfamily 1 (SF1) group of helicases [160]. The remaining portion (~471–791 aa) holds the protease domain, which can be separated into two smaller sections. The first section bears a papain-like cysteine protease domain (~471–605 aa), while the last section appears to be a non-functional Ftsj (rrmj) methyltransferase-like domain (~606–791 aa) [160].

This multi-functional nsP2 is capable of performing at least four enzymatic functions. The helicase activity is only functional when the full length nsP2 is available, even though the effector domains are found on the N terminus [160]. Truncated recombinant proteins were found to be inactive [161]. The CHIKV nsP2 is only able to unwind double-stranded RNA that have a 5' overhang of at least 12 bp in and also only in the 5'–3' directionality [160]. Since it possesses RecA-like domains, it is not surprising that it facilitates the complementary base-pairing of single-stranded RNA [160]. The CHIKV nsP2 has also been reported to display nucleotide triphosphatase (NTPase) activities and is able to hydrolyse all dNTPs and NTPs without any preference. However, this is observed only in full length nsP2 [160,161]. Furthermore, the activation of the NTPase of the nsP2 by RNA and DNA oligonucleotides is, again, only possible with the full length nsP2 [160]. Interestingly, the same active site used for the NTPase activity has also been found to perform RNA 5' triphosphatase activities, the third function, which mediates the cleavage of γ -phosphates from RNA substrates [161]. The last known enzymatic function is the protease activity of the nsP2, which is responsible for processing of the nsP polyprotein [162,163].

Apart from these enzymatic functions, the nsP2 has been long known to enter the host nucleus during infection, albeit with the absence of any putative nuclear localization signals [147,164]. Although the exact mechanism is still unknown, the localization of nsP2 is essential in inhibiting the host antiviral responses [165–167]. One interesting observation reported by Fros and colleagues is that CHIKV nsP2 can be detected in the nuclear region at 4 h post infection (h.p.i) before translocating to the cytoplasm at a later time point of 12 h.p.i [168]. One way that the CHIKV nsP2 is able to induce the shutdown of host transcription is by mediating the degradation of a catalytic subunit of the RNA polymerase II, Rpb1 [169]. The nsP2 protein has also been found to be responsible for the suppression of the host cellular translation processes without affecting viral protein translation [53]. Interactions of the alphavirus nsP2 protein with a large number of ribosomal proteins and proteins that are involved in translations have also been revealed via immunoprecipitation assays [170]. For instance, in VEEV, the ribosomal protein S6 (RpS6) was found to immunoprecipitated with nsP2 in both mammalian and insect cells [171]. Low levels of RpS6 proteins have been correlated strongly with diminished cellular translation activities [171]. However, the exact mechanism of this dephosphorylation phenomenon is still unknown. Recently, nsP2 and nsP3 were also discovered to exhibit RNA interference activity [172].

The promiscuous alphavirus nsP2 is able to bind to not only the other nsPs but also a number of host factors. The interactions with nsPs were confirmed for CHIKV through immunoprecipitation of GST and streptavidin-tagged nsPs and their various domains, and validated via a yeast two-hybrid screen and ELISA [173,174]. In addition, using computational techniques, Rana and colleagues were able to propose a spatial model of the late CHIKV replication complex [173]. Bourai and colleagues performed an extensive study on the host factors interacting with the nsP2 using a yeast two-hybrid screen [175]. While they identified 22 unique hits, only heterogeneous nuclear ribonucleoprotein K

(hnRNP-K) and ubiquilin 4 (UBQLN4) were observed to play a significant role in CHIKV replication upon gene silencing [175]. Another host factor, the NDP52 human autophagy receptor, was shown to interact with CHIKV nsP2 and acts as a pro-viral factor in human cells [176,177]. Although the precise mechanism is still unknown, it has been postulated that the human NDP52 interacts with nsP2 in the cytoplasm to prevent the latter from localizing into the nucleus. This could in turn delay cell death, which would allow more time for the CHIKV to replicate [147]. The nsP2 is also implicated in the suppression of the unfolded protein response (UPR) triggered by the production of CHIKV envelope proteins in the endoplasmic reticulum (ER) [168]. Although the exact mechanism of action remains to be clarified, incomplete splicing of the X-box binding protein 1 (XBP1) mRNA (complete splicing is required for UPR) has been observed in cells transfected with nsP2 [168].

Being such a multifunctional protein that is involved in a number of important processes such as viral genome replication and host evasion, CHIKV nsP2 presents an intriguing and promising target for drug development. This has been aptly reviewed by Bakar and Ng [178].

4.3. Nonstructural Protein 3 (nsP3)

The nsP3 (530 amino acids, ~60 kDa) protein possesses three domains, a highly conserved N-terminal macro domain (~160 aa), followed by a zinc²⁺ binding domain (~165 aa) and ends with a variable “tail” region (~205 aa) [58,144,147]. The macro domain contains a ubiquitous protein module found in all living organisms including positive sense RNA viruses like alphaviruses, coronaviruses, hepatitis E virus and rubella virus [179]. The macro domain is believed to function mainly as an ADP hydrolase that removes mono or poly ADP-ribose marks on proteins. ADP-ribose marks usually occur on Asp, Glu, and Lys residues and are indicative of post-translational modifications by the poly (ADP-ribose) polymerases (PARPs) [180,181]. In experiments involving mass spectrometry, McPherson and colleagues discovered that the CHIKV nsP3 is able to recognize and hydrolyse the ADP-ribose groups from mono ADP-ribose marks that found on only Asp and Glu residues [182]. The authors went on to show that the loss of the hydrolase significantly compromised the ability of CHIKV to replicate in both baby hamster kidney and *Aedes albopictus* cells [182]. Moreover, CHIKV infectious clones encoding hydrolases with impaired activities were found to replicate more slowly in mouse neuronal NSC-34 cells with a significant decrease in fitness in neonate mouse model [182]. These results indicate that the macro domain of nsP3 proteins plays an important role in the viral replication and virulence of the CHIKV. In addition, it also suggests that the levels of ADP-ribosylation could play a major role in the anti-viral response by the host.

The zinc binding domain of CHIKV nsP3 was inferred from the crystal structure of the SINV by Shin and colleagues [158]. Mutations in this region resulted in the impairment of both the negative-sense and 26S subgenomic RNA synthesis and polyprotein processing in SINV [183,184]. Similarly, mutations in the zinc-binding region of SFV nsP3 resulted in defects in neurovirulence [185]. However, little is known about their precise mechanisms.

The stretch of conserved residues (proline-rich) on the variable “tail” region was found to be able to bind to the host amphiphysin1 and 2 proteins through the Src-homology 3 (SH3) domains found on the amphiphysin proteins [186,187]. This phenomenon is observed readily upon the transfection of the CHIKV nsP3. Although no validation was performed using CHIKV infected cells, both SFV and SINV infected cells confirmed this observation [186]. Amphiphysins are postulated to be involved in the formation of the spherules (which house replication complexes) given their ability to induce membrane curvature [147,186,188].

The nsP3 also binds to GTPase-activating protein (SH3 domain)-binding protein 1 (G3BP1) and its homolog (G3BP2). The G3BPs are found in stress granules, which are believed to have anti-viral properties. For instance, stress granules are involved in the inhibition of RNA translation [147]. By sequestering the G3BPs, the nsP3 is able to prevent stress granules from forming during infection [189–191]. However, the depletion of the G3BPs was found to be unfavorable for CHIKV replication [192–194]. The proposed pro-viral activity of the G3BPs includes aiding the switch from the

translation of non-structural proteins to viral RNA replication [192–194]. In mosquito cells, the G3BP homolog, Rasputin (Rin), was found to also exhibit similar phenomenon [195]. However, in cell culture, the silencing of Rin did not adversely affect CHIKV replication [195]. Instead a significant reduction in total infectious viral titer was observed in *Aedes albopictus* in vivo [195]. Interestingly, Remenyi and colleagues also showed that nsP3 is closely associated with the host cellular lipid droplets and also with nsP1 [196].

Sphingosine kinase 2 (SK2) was reported to co-localize with nsP3 in nsP3 overexpression studies. In addition, SK2 also colocalizes with the CHIKV RNA [197]. Moreover, Reid and colleagues showed that upon SK2 knockdown, there was a significant reduction in infectious viral titer, suggesting a pro-viral role [197]. However, the exact mechanism still remains to be solved. Additionally, there are other host factors (Y-Box-Binding Protein 1 (YBX1), PI3K-Akt-mTOR pathway, DDX1/DDX3, and IKK β) that were reported to be able to bind or interact with the alphavirus (SINV, SFV, and VEEV) nsP3 reviewed Lark and colleagues [198]. However, these have not been validated for CHIKV. Another pro-viral host protein found to co-immunoprecipitate with the nsP3 is the heat shock protein 90 β (Hsp90 β), but its exact function is unknown [199].

4.4. Nonstructural Protein 4 (nsP4)

The bulk of the nsP4 (611 aa, ~70 kDa) protein consists of an RNA-dependent RNA polymerase (RdRp) (~500 aa), with the characteristic GDD motif, responsible for viral RNA synthesis at its C-terminus [58,144,147]. The remaining ~100 aa at its N-terminus, despite being a relatively unknown and seemingly intrinsically disordered stretch of sequences, is still important for the normal function of the nsP4 in SINV [200]. To date, high resolution structures of the CHIKV RdRp are still not available. Recently, Chen and colleagues were able to generate a truncated but soluble, well-folded, functional RdRp catalytic subunit from *E. coli* [201]. They showed that the CHIKV RdRp has a preference for single-stranded RNA with a 5'-overhang that is of at least 4 nucleotides long [201]. In addition, the RdRp was also found to be rather sensitive to a number of detergents in comparison to the relatively resilient Dengue virus RdRp [201]. The RdRp was also able to exhibit primed extension of templates and terminal adenylyltransferase (TATase) activity regardless of the presence of any template [201].

Similar to the nsP3 protein, the nsP4 protein was found to interact with another Hsp90 protein, Hsp90 α . Inhibition of Hsp90 α resulted in a decrease in both viral RNA and protein levels [199]. However, the mechanism of the interaction remains to be discovered. In another study, Rathore and colleagues showed that overexpression of the CHIKV nsP4 was able to suppress the phosphorylation of eukaryotic translation initiation factor, alpha subunit (eIF2 α), which in turn antagonizes the host unfolded protein response during infection [202]. On the other hand, during SINV infection, rapid phosphorylation of eIF2 α was observed instead. However, the mechanism behind this interaction remains unexplored.

An in-depth review on the nsP4 functions and interactions was also recently published by Pietila and colleagues [203].

5. Other Host Factors That Are Involved in CHIKV Replication Cycle

In concert with the above efforts, a number of host factors have been identified via different screening methods. For instance, Paingankar and colleagues discovered that CHIKV interacts with housekeeping proteins like that actin, heat shock protein 70 (HSP70) and STAT2 (Vero-E6 cells only) via virus overlay protein binding assay (VOPBA) complemented with matrix-assisted laser desorption/ionization time of flight analysis (MALDI TOF/TOF) [204]. They went on to show that the silencing of HSP70 resulted in a significant decrease in total infectious viral titer. However, the exact mechanism remains to be solved.

Treffers and colleagues employed the use of stable isotope labeling with amino acids in cell culture (SILAC) coupled with liquid chromatography–mass spectrometry (LC-MS) to uncover the

temporal dynamics of the cellular response during CHIKV infection [205]. They were able to pick up 13, 38, and 106 proteins that were differentially expressed at 8, 10, and 12 h.p.i, respectively. Moreover, majority of the proteins detected were the subunits of RNA polymerase II, and they were found to be progressively degraded [205]. This is in line with the observation that cellular transcriptional shut off occurs during CHIKV. The authors also reported four anti-viral factors (Rho family GTPase 3 (Rnd3), DEAD box helicase 56 (DDX56), polo-like kinase 1 (Plk1), and ubiquitin-conjugating enzyme E2C (UbcH10)), which were down regulated during CHIKV infection [205]. However, the exact mechanisms remain to be discovered.

A very extensive human whole genome siRNA mediated loss-of-function screen was recently performed in a bid to identify effective therapeutics against CHIKV [206]. Karlas and colleagues were able to capture 156 pro-viral and 41 antiviral host factors that affect CHIKV replication [206]. They performed pathway analysis of the identified pro-viral factors and subsequently identified 21 FDA-approved small-molecule inhibitors that were effective against CHIKV by cross referencing with specialized databases [206]. These 21 antiviral compounds were found to act on four host factors (vacuolar-type H⁺ ATPase (vATPase), CDC-like kinase 1 (CLK1), fms-related tyrosine kinase 4 (FLT4 or VEGFR3), and the K (lysine) acetyltransferase 5 (KAT5 or TIP60)) and two pathways (calmodulin signalling and fatty acid synthesis) [206]. Through in vivo and in vitro work, three of the inhibitors (Tivozanib, Pimozide, and 5-tetradecyloxy-2-furoic acid (TOFA)) were reported to exhibit prophylactic antiviral effects in mice [206]. In addition, when the authors combined two inhibitors (Pimozide and TOFA), each targeting the calmodoulin signalling and fatty acid synthesis pathways, respectively. The synergistic effect resulted in a therapeutic antiviral effect in both in vivo and in vitro studies [206]. However, the exact mechanism and role played by these host pathways in CHIKV replication warrants further work. Nonetheless, the work by Karlas and team showed the importance and relevance of understanding the interplay of host factors during viral infection, as well as the significant translational value that can be gained from performing basic research on the importance of host factors during CHIKV infection.

6. Conclusions and Perspectives

Even though a large number of host factors have been identified through these studies (Table 1), the mechanistic details of the interplay of the host factors during CHIKV infection are still lacking. The advantages of targeting host factors are plenty, as opposed to targeting just viral proteins. For instance, targeting host factors may allow inhibition of a broad-spectrum of viruses that share same host factors (Table 1). Moreover, those drugs could also be tested for synergistic effects with specific viral protein inhibitors for development of a more comprehensive treatment plan that targets multiple pathways. This therapeutic approach would also prevent the development of antiviral resistance. For instance, small molecule inhibitors that mimic the interaction sites found on GAGs, PHB, TIM, and TAMs could be developed. These would bind to CHIKV, drastically reduce the opportunity for the CHIKV to interact with the attachment factors present on the host cells and hence dampen its infectivity. Similarly, this approach could also be extended to host factors that are involved in the CHIKV replication cycle like the NDP52 host protein and given in a cocktail to patients.

A promising cocktail candidate for clinical trials would be the combination of Pimozide and TOFA concocted by Karlas and team. In drug research, though many drugs screened may have shown to possess great efficacy in vitro, many of them failed during the in vivo validation processes. On the other hand, the cocktail of Pimozide and TOFA was able exhibit impressive efficacy in both in vitro and in vivo studies. Therefore, we feel that there is great potential in this combination host-targeting drug therapy.

Table 1. Summary of host factors known to interact with CHIKV proteins.

Viral Protein	Validated Interacting Host Factors/Pathways	Known Functions of Host Proteins	Putative Function/Interaction with CHIKV Postulated by the Authors	Examples of Interaction with Other Medically Important RNA Viruses	References
Capsid	Kar α 4 (KPNA4)	Karα4 (KPNA4): A group of proteins that transport molecules between the cytoplasm and nucleus. Able to act as either importins or exportins.	Karα4 (KPNA4): Binds to NLS of CHIKV capsid protein for nuclear translocation.	Karα4 (KPNA4): Proposed to Interact with Middle East Respiratory Syndrome (MERS) virus protein OF4b to prevent NF-kappa-B complex from entering the nucleus.	[113,207]
	CRM1 (XPO1)	CRM1 (XPO1): Major mammalian export protein that facilitates export of RNA and proteins from the nucleus to the cytoplasm.	CRM1 (XPO1): Pro-viral factor. Binds to the NES/ of capsid, allowing exit from the nucleus.	CRM1 (XPO1): Proposed to bind and export the following RNA-containing viral proteins from the nucleus to the cytoplasm: human immunodeficiency virus (HIV) Rev protein cargo complex, human T-cell leukemia virus type 1 (HTLV-1) rex protein, and influenza A ribonucleoprotein complexes.	[113,208–213]
E3	Furin	Furin: Calcium-dependent serine endoprotease. Preferentially cleaves at sites with paired basic amino acids.	Furin: Cleaves the E3 protein away from the precursor E2 polyprotein.	Furin: Shown to be essential for H5N1, H7N1 avian influenza viruses, and Canine distemper virus (CDV). Actual mechanism unknown.	[106,118,214]
E2	PHB	PHB: Many reported functions, including modulation of transcription and chaperone functions in the mitochondria.	PHB: Possible attachment/entry factor.	PHB: Shown to interact with HIV-1 glycoprotein, and the binding is important for its replicative spreading in cells. Interacts with dengue virus E protein and is the first characterized receptor protein for dengue virus in insect cells. Proposed to be entry factors for hepatitis C virus.	[124,215–217]
	PTPN2	PTPN2: A tyrosine phosphatase that dephosphorylates protein tyrosine kinases in both nuclear and cytoplasm compartments. Involved in numerous signaling events (e.g., endocytic recycling).	PTPN2: Postulated to be involved in transportation of viral structural proteins to host plasma membrane.	PTPN2: Hepatitis C virus nonstructural 3/4A protease cleaves PTPN2 that induces a shift from host Th1 to Th2 immune response.	[128,218]
	COL1A2	COL1A2: A group 1 collagen found in most connective tissues.	COL1A2: Mechanism unknown.	COL1A2: Shown to increase infectious viral titer of Sindbis virus (SINV) and also proposed to aid in its transmission.	[128,219]
	ACTG1	ACTG1: Part of cellular trafficking machinery.	ACTG1: Postulated to be involved in transportation of viral structural proteins in host cell.	ACTG1: The human immunodeficiency virus type 1 (HIV-1) protease was found to cleave actin (ACTG1).	[128,220]

Table 1. Cont.

Viral Protein	Validated Interacting Host Factors/Pathways	Known Functions of Host Proteins	Putative Function/Interaction with CHIKV Postulated by the Authors	Examples of Interaction with Other Medically Important RNA Viruses	References
	GAGs	GAGs: A group of complex linear polysaccharides expressed on cell surface, in intracellular compartments, and also in the extracellular environment, where they are able regulate many cellular processes including (examples cell signaling, etc.).	GAGs: Possible attachment/entry factor.	GAGs: Allows binding and infection of hepatitis B virus. Attachment factor for respiratory syncytial virus (RSV), coronavirus NL63 (CoV-NL63), and the severe acute respiratory syndrome coronavirus (SARS-CoV).	[132,221–225]
	hTIM1	hTIM1: Involved in regulation of both innate and adaptive immune responses, engulfment of apoptotic cells, and T cell—proliferation.	hTIM1: Possible attachment/entry factor.	hTIM1: Implicated as receptors for non-enveloped hepatitis A virus and enveloped viruses such as Zaire Ebola virus and Lake Victoria Marburg virus.	[129,226–228]
	AXL receptor tyrosine kinase	AXL: Regulate and involved in many important physiological processes like cell proliferation, survival, differentiation, and migration.	AXL: Possible attachment/entry factor.	AXL: Implicated as receptors for Ebola virus, Marburg virus, pseudo-typed lentiviral, vaccinia virus, and Lassa virus.	[129,229–231]
6K/TF	-	-	-	-	-
	COMMD1	COMMD1: A proposed scaffold protein that is involved in diverse physiological processes. Able to regulate the ubiquitination and degradation of specific cellular proteins including NF- κ B subunit p65.	COMMD1: Postulated to be involved in transport of viral structural proteins in host cell and/or involved in regulating host immune response.	COMMD1: Enhances latent infection of HIV-1 by stabilizing I κ B- α , the inhibitor of NF- κ B, and attenuating innate immune response.	[128,232,233]
	THBS1	THBS1: Adhesive glycoprotein that binds heparin. Plays a role in dentinogenesis via its anti-angiogenic properties. Also suggested to play a role in ER stress response.	THBS1: Mechanism unknown.	THBS1: Induced by hepatitis C virus (HCV) to promote the proteolytic activation TGF- β 1, which promotes HCV RNA replication.	[128,234]
E1	DYNC1H1	DYNC1H1: Subunit of dynein complex. Integral part of cellular transport machinery across cells including neuronal cells. Plays a role in mitotic spindle and metaphase plate assembly.	DYNC1H1: Postulated to be involved in transport of viral structural proteins in host cell and implicated in neurological manifestations of CHIKV.	DYNC1H1: Aids in uncoating of HIV-1 nucleocapsids during infection. Proposed to be involved in the transport of influenza virus X-31, human foamy virus (HFV), HIV1 reverse transcription complexes (RTC), herpes simplex virus type 1, and Mokola virus.	[128,235,236]
	ATP1B3	ATP1B3: Part of the sodium/potassium-transporting ATPase that maintains electrochemical gradient and is important for osmoregulation.	ATP1B3: Probably facilitates fusion of viral envelope to host membrane during viral entry.	ATP1B3: Shown to inhibit enterovirus 71 (EV71) replication by up-regulating type-I interferon production. Proposed to be a pro-viral factor for HIV-1 by accelerating the degradation of BST-2.	[128,235,236]

Table 1. Cont.

Viral Protein	Validated Interacting Host Factors/Pathways	Known Functions of Host Proteins	Putative Function/Interaction with CHIKV Postulated by the Authors	Examples of Interaction with Other Medically Important RNA Viruses	References
	BST-2	BST-2: Lipid-raft associated protein that is part of the antiviral response pathway. Blocks the release of many enveloped mammalian virus by tethering the mature virions to the cell plasma membrane of the infected cells.	BST-2: Proposed to restrict virus release by latching onto the CHIKV E1 protein.	BST-2: Restricts Lassa virus replication and release. Restricts viral like particle (VLP) release of the following viruses: vesicular stomatitis virus (VSV), hepatitis C virus (HCV), Kaposi's sarcoma-associated herpesvirus (KSHV), human immunodeficiency virus 1 (HIV-1), ebola virus, Machupo virus MACV) Nipah virus, Zaire ebolavirus (ZEBOV), Lake Victoria marburgvirus (MARV), Rift Valley fever virus (RVFV), cowpox virus (CPXV), and influenza virus.	[142,143,237–244]
nsP1	BST-2	BST-2: See above.	BST-2: nsP1 reverses BST-2 ability to restrict virus release by down-regulating the latter's expression.	BST-2: See above.	[142,143,156]
	Rpb1	Rpb1: A catalytic subunit of the RNA polymerase II complex that catalyses RNA transcription.	Rpb1: Does not get degraded by the CHIKV nsP2 proteins. Instead is degraded via nsP2 mediated ubiquitination.	Rpb1: Same observations were found in Sindbis, Semliki Forest virus (old world alphaviruses).	[169]
nsP2	SFRS3/SRp20 (Serine and Arginine Rich Splicing Factor 3)	SFRS3 (SRp20): RNA splicing factor, aids in exon-inclusion during alternative splicing. Involved in mRNA nuclear export.	SFRS3 (SRp20): Mechanism unknown.	SFRS3 (SRp20): Proposed to be crucial for IRES-mediated translation in poliovirus.	[175,245]
	VIM (Vimentin), TACC3 (transforming, acidic coiled-coil containing protein 3), CEP55 (centrosomal protein 55 kDa), and KLC4 (kinesin light chain 4)	VIM, TACC3, CEP55, and KLC4: Cytoskeletal components.	VIM, TACC3, CEP55 and KLC4: Proposed to be hijacked by nsP2 for transport into the infected cells. Interaction with CHIKV nsP3 was also reported and is proposed to aid in the anchorage of the replication complex.	VIM: Proposed to be involved in the distribution and acidification of endosomes, allowing successful release of influenza A viral genome. TACC3, CEP55, KLC4: Not reported.	[175,246,247]

Table 1. Cont.

Viral Protein	Validated Interacting Host Factors/Pathways	Known Functions of Host Proteins	Putative Function/Interaction with CHIKV Postulated by the Authors	Examples of Interaction with Other Medically Important RNA Viruses	References
	<p>ASCC2 (activating signal cointegrator 1 complex subunit 2), TRIM27 (tripartite motif 27), MRFAP1L1/MRG15 (Morf4 family-associated protein 1-like 1), EWSR1 (Ewing sarcoma breakpoint region 1), IKZF1 (IKAROS family zinc finger 1) and ZBTB43 (zinc finger and BTB domain-containing 43)</p>	<p>ASCC2: Proposed to regulate/involved in DNA transcription and repair. TRIM27: Represses gene transcription through ubiquitination. MRFAP1L1/MRG15: Proposed to regulate transcription by interacting with both the retinoblastoma tumor suppressor (Rb) and a nuclear protein PAM14 (protein associated with MRG, 14 kDa). EWSR1: Proposed to be involved in gene expression, cell signaling, and RNA processing and transport. IKZF1: A transcription factor that is associated with chromatin remodeling. ZBTB43: Proposed to suppress transcription of Blimp1 [PR domain zinc finger protein 1] (a transcription factor for various innate and adaptive immune cell types).</p>	<p>ASCC2, TRIM27, MRF4P1L1, EWSR1, IKZF1, and ZBTB43: Mechanism unknown.</p>	<p>ASCC2: Not reported. TRIM27: Interacts and is degraded by the immediate early protein ICP0 of the herpes simplex virus 1 (HSV-1). However, depletion of TRIM27 in cells results in reduced virus titer. MRFAP1L1: Not reported. EWSR1: Binds directly with the <i>cis</i>-acting replication element (CRE) of hepatitis C virus. Depletion of EWSR1 impairs HCV viral replication and reduced virus titers without affecting translation. IKZF1: Not reported. ZBTB43: Not reported.</p>	<p>[175,248–250]</p>
	<p>HNRNPK</p>	<p>HNRNPK: Binds to cytidine-rich pre-mRNA. Proposed to play a role in hnRNA metabolism. Plays an important role response to DNA damage via P53 pathway. Able to activate and repress transcription.</p>	<p>HNRNPK: Mechanism unknown.</p>	<p>HNRNPK: Proposed restrict HCV replication by limiting the availability of the HCV RNA for packaging into virions. Demonstrated to support vesicular stomatitis virus (VSV) infection via (1) suppression of apoptosis in infected cells, (2) inhibiting antiviral protein expression, and (3) supporting the expression of several cellular proteins necessary for the virus.</p>	<p>[175,251,252]</p>
	<p>TTC7B (Tetratricopeptide repeat domain 7B)</p>	<p>TTC7B: Part of a complex that regulates and localizes phosphatidylinositol 4-kinase. (PI4K) to the cell plasma membrane.</p>	<p>TTC7B: Aids nsP2 in shutting off host cellular processes.</p>	<p>TTC7B: Dengue 2 virus induce expressions of proteins that contain tetratricopeptide repeats (TTC).</p>	<p>[175,253,254]</p>

Table 1. Cont.

Viral Protein	Validated Interacting Host Factors/Pathways	Known Functions of Host Proteins	Putative Function/Interaction with CHIKV Postulated by the Authors	Examples of Interaction with Other Medically Important RNA Viruses	References
	<p>UBQLN4, RCHY1 (ring finger and CHY zinc finger domain-containing 1), and WWP1 (WW domain-containing E3 ubiquitin protein ligase 1)</p>	<p>UBQLN4, RCHY1, and WWP1: Involved in autophagy and/or protein degradation</p>	<p>RCHY1 and WWP1: Mechanism unknown. UBQLN4: Pro-viral factor. Mechanism unknown.</p>	<p>RCHY1: Interacts with SARS nonstructural protein 3 to increase degradation of P53, which is involved in innate antiviral immunity. WWP1: Aids in budding of ebola virus VP40 matrix protein via ubiquitination of the matrix proteins. UBQLN4: Shown to interact with small hydrophobic (SH) protein of mumps virus and relocate them to 20S proteasome, possibly for proteosomal degradation.</p>	[175,255–257]
	<p>PDK2 (pyruvate dehydrogenase kinase, isozyme 2), RBM12B (RNA-binding motif protein 12B), GFAP (glial fibrillary acidic protein), and TPR (translocated promoter region [to activated MET oncogene])</p>	<p>PDK2: Phosphorylate pyruvate dehydrogenase subunits to regulate glucose and fatty acid metabolism and homeostasis. Regulate cell proliferation and delay apoptosis when cells are under oxidative stress. RBM12B: RNA-binding protein GFAP: A type of intermediate filament (class-III) and is a cell-specific marker that helps to differentiate astrocytes from other glial cells during the development of the central nervous system. TPR: A scaffolding component found on the nuclear face of the nuclear pore complex. Allows transport of proteins and mRNAs out of the nucleus. Also aids in perinuclear chromatin distribution.</p>	<p>PDK2, RBM12B, GFAP, and TPR: Mechanism unknown.</p>	<p>PDK2: Not reported. RBM12B: Not reported. GFAP: Measles virus disrupts the glial-fibrillary-acidic protein filament (GFAP) network in Astrocytoma Cell Line (U-251). Exact function is unknown. TPR: Suppressed by the Avian reovirus (ARV) protein p17 Knock-down of TPR has shown to increase ARV titer.</p>	[175,258–260]
	<p>NDP52/CALCOCO2 (calcium-binding and coiled-coil domain-containing protein 2)</p>	<p>NDP52: Involved in autophagy; recruits and degrades intracellular pathogens and is able to inhibit proliferations of pathogens like Salmonella.</p>	<p>NDP52: Seems to be able to recruit CHIKV nsP2 and LC3C to the trans-Golgi network that contains double-stranded RNA and other nsPs. This is postulated to allow formation of the replication complexes, thereby promoting viral infection.</p>	<p>NDP52: Proposed to modulate innate immune response upon interacting with influenza virus protein PB1-F2.</p>	[175–177,261,262]

Table 1. Cont.

Viral Protein	Validated Interacting Host Factors/Pathways	Known Functions of Host Proteins	Putative Function/Interaction with CHIKV Postulated by the Authors	Examples of Interaction with Other Medically Important RNA Viruses	References
nsP3	PI3K-Akt-mTOR pathway	PI3K-Akt-mTOR pathway: Regulates cell cycle and is directly involved in cellular proliferation, quiescence, and cancer.	PI3K-Akt-mTOR pathway: Drives the internalization of the replication complex.	PI3K-Akt-mTOR pathway: Essential for survival of host and virus (Hepatitis C Virus, Vaccinia, and Cowpox Virus).	[75,263,264]
	G3BP1 & G3BP2	G3BP1: Marker for stress granules and may be an effector for stress granule assembly. Able to unwind DNA and RNA. G3BP2: Postulated to be a scaffold protein which could transport mRNA.	G3BP1 & G3BP2: Colocalizes with nsP2 and nsP3. Depletion of both proteins results in reduction of viral RNA (especially the negative sense RNA), proteins, and infectious titer. Authors proposed that the G3BPs could mediate the switch from translation to amplification of viral genome.	G3BP1: Knock-down of G3BP1 results in an increase in HIV-1 viral titer only in primary T cells and macrophages. Found to interact with HIV-1 RNA in the cytoplasm. G3BP1 is proposed to sequester viral RNA transcripts, preventing translation and packaging. G3BP1 and G3BP2: DENV-2 non-coding subgenomic flaviviral RNA (sfRNA) was found to bind to both G3BP1 and G3BP2 and inhibit their antiviral activities.	[192,265,266]
	SK2	SK2: A lipid kinase that phosphorylates sphingosine to form sphingosine 1-phosphate (SPP). Involved in cell differentiation, growth, and host immunity.	SK2: Colocalizes with CHIKV RNA and nsPs. Knock-down of SK2 inhibits CHIKV infection.	SK2: Not reported.	[197]
	Hsp90β	Hsp90β: A cytoplasmic isoform of HSP-90s molecular chaperons that is constitutively expressed. They are able to modulate different cellular processes (e.g., refold proteins) to maintain cellular homeostasis.	Hsp90β: Mechanism unclear. Proposed to have an ancillary role in CHIKV replication. On a side note, Hsp90 is proposed to stabilize CHIKV nsP2 during infection.	Hsp90β: Proposed to be the binding receptor for Japanese encephalitis virus (JEV). Proposed to facilitate assembly of enterovirus 71 viral particles. Hepatitis B virus polymerase interacts with Hsp90β to suppress NF-κB signaling.	[199,267–270]
	LCPI (Lymphocyte cytosolic protein 1/L-Plastin)	LCPI: Binds to actin and aids in activation of T-cells during co-stimulation through other receptors.	LCPI: Mechanism unknown.	LCPI: Not reported.	[175]

Table 1. Cont.

Viral Protein	Validated Interacting Host Factors/Pathways	Known Functions of Host Proteins	Putative Function/Interaction with CHIKV Postulated by the Authors	Examples of Interaction with Other Medically Important RNA Viruses	References
	Hsp90 α	<p>Hsp90α: A cytoplasmic isoform of HSP-90s molecular chaperons that is produced during cell stress response. They are able to modulate different cellular processes (e.g., refold proteins) to maintain cellular homeostasis.</p>	<p>Hsp90α: Proposed to help in stabilizing CHIKV nsP4 and aid in formation of CHIKV replication complex in the cytosol. Knock-down of Hsp90α resulted in a decrease in viral RNA.</p>	<p>Hsp90α: Not reported.</p>	[199]
	eIF2 α	<p>eIF2α: A eukaryotic initiation factor that is essential for initiating translation.</p>	<p>eIF2α: nsP4 suppresses the serine-51 phosphorylation of eIF2α, which in turn regulates the PERK pathway, allowing the CHIKV to overcome the host unfolded protein response machinery.</p>	<p>eIF2α: The presence of the three rotavirus proteins, VP2, NSP2, and NSP5, induces the phosphorylation of eIF2α. However, formation of stress granules (which stalls translation) was inhibited. HSV utilizes its neurovirulence factor ICP34.5 to dephosphorylate eIF2α.</p>	[202,271,272]

It should still be noted that targeting host factors comes with the risk of toxicity, especially when these host factors perform vital functions in the host cells. Design of therapeutics therefore needs to be optimized to target interactions between host and viral factors, while minimizing disruption of essential cellular processes. With the significant bottlenecks in our knowledge of basic CHIKV virology and its interacting host partners, more research is needed to understand the molecular mechanisms of the interactions between the CHIKV and its host factors. This would not only help to increase the knowledge pool but also provide more opportunities and avenues to develop, optimize, and/or speed up the production or repurposing of potential therapeutics to combat this medically important re-emerging arbovirus.

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