

Treatment of Chikungunya Virus (CHIKV) Using Targeted Immunotherapy

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Abstract

Chikungunya virus (CHIKV) is the most common mosquito-borne *Alphavirus* infecting humans worldwide. Up to date, there are no antiviral treatments or vaccines approved to treat or prevent CHIKV for which treatments remain symptomatic based on clinical manifestations. Hence, designing effective therapies to either prevent or treat CHIKV infection is of paramount importance. Interestingly, monoclonal antibodies (mAbs) are known to be significantly important in mediating protective immunity in CHIV infection. During the last decades, numerous animal studies have reported the protective and prophylactic efficacy of human and mouse anti-CHIKV mAbs isolated from convalescent patients. However, the therapeutic benefits of these anti-CHIKV mAbs can be limited by multiple factors. Thus, it becomes pertinent to better understand the CHIKV infection dynamics, mitigate the undesired mAbs-associated effects and improve therapies. In this review, we critically discuss CHIKV antiviral infectious mechanisms and address how the improved understanding of the latter may pave the way to better targeted immunotherapies.

Keywords: Therapeutics, Antibodies, Vaccines, Prophylactics, Chikungunya virus

1. Introduction

Chikungunya virus (CHIKV) is an arthropod-borne virus firstly discovered during the Tanzanian outbreak in 1952 and isolated a year later (1953) from patient serum and mosquitoes [1]. CHIKV is a worldwide epidemic threat responsible for self-limited fever, maculopapular rashes, and debilitating polyarthralgia in most (90–92%) infected patients [1, 2]. Its name, meaning “that which contorts or bends up” in “Kimakonde”, a Tanzanian and Mozambican vernacular language, stems from the stooped posture exhibited by infected patients [3–6]. In endemic areas, CHIKV can be misdiagnosed as it displays dengue (DENV) or zika virus (ZIKV) like symptoms [1, 7]. Although less lethal, CHIKV-associated mortality rate can be influenced by other factors, including immunocompromised individuals, newborns from high viremic mothers or patients with preexisting arthritis [1]. CHIKV represents a serious economic burden, affecting the physical status of infected

patients, restraining them from working for up to 35 days, as reported during the 2007 Indian outbreak [8]. For that reason, CHIKV was categorized as a biodefense pathogen by the National Institute of Allergy and Infectious Diseases (NIAID) in the USA [9]. Presently, there are no clinically licensed vaccines or therapies to treat CHIKV. Nonetheless, several pre-clinical animal models using antibody-based immunotherapy have shown some promising results in preventing and treating CHIKV infections [1, 7, 9, 10]. Despite several obstacles that have to be overcome to reach clinical fruition of such therapy [11], mAbs therapies offer better therapeutic avenues with respect to emerging disease outbreaks [12]. Hence, this review succinctly describes CHIKV characteristics (Transmission, structure and diagnosis) and highlights the potential therapeutic usage of mAbs based on their protective role in naturally occurring humoral immunity following CHIV infection. Lastly, we briefly discuss some challenges associated with mAbs therapy and propose future alternative therapeutic approaches.

2. Chikungunya's transmission cycle

CHIKV can be transmitted either horizontally from human to human through mosquito bites (*Aedes* species) [1] or vertically from a mother to a child during pregnancy or at birth, thus causing severe neonatal infection [1, 13, 14]. However, the rate of CHIKV transmission can be affected by the geographical location and the vector. It has been historically reported that CHIKV was predominant in Sub-Saharan Africa (SSA), Southeast Asia tropical and sub-tropical regions, where two different transmission cycles occur [15]. In rural areas, CHIKV replicates through a sylvatic transmission cycle (animal to human transmission via the mosquito), involving forest or savanna *Aedes* mosquitoes (*A. furcifer* and *A. africanus*) and animals (domestics and non-domestics), representing the main CHIKV reservoirs within this cycle [16]. The urban transmission cycle is mediated by *A. albopictus* (also known as Asian tiger mosquito) and *A. aegypti*, both maintaining the human-to-human transmission, thus making humans the principal CHIKV reservoirs in the urban epidemic cycle (Figure 1). Interestingly, Chikungunya fever outbreaks in Asia have been associated with only the

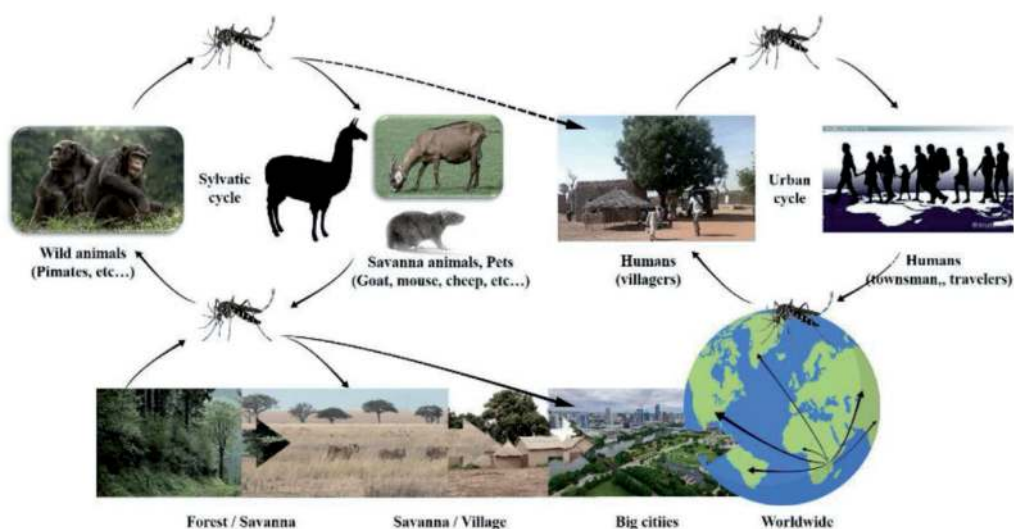


Figure 1. CHIKV transmission cycle: Two cycles known as sylvatic and urban characterized the CHIKV transmission cycle. While the sylvatic predominantly occurs in Africa and circulates between primates, rodents and other vertebrates, the urban counterparts is commonly observed in Asia, where CHIKV is horizontally transferred from human to human through mosquito bites or blood meal.

urban CHIKV transmission cycle, while the African counterparts are related to both sylvatic and urban transmission cycles [15, 17]. Based on this evidence, it can hypothetically be suggested that the CHIKV transmission cycle before 1952 was restricted to the sylvatic cycle and that its urban transmission resulted from demographic expansion through deforestation or migration of CHIKV infected travelers from rural to the most populated urban cities. While the natural factors sustaining CHIKV infection remain elusive [16], it can be hypothesized that simultaneous presence of *Aedes* specie mosquitoes and CHIKV carriers (even with very low viral load in the blood) in a given area is enough for the resurgence of CHIKV-associated outbreaks.

3. Clinical manifestations of chikungunya fever

Chikungunya virus (CHIKV) is an emerging and re-emerging arbovirus associated with high morbidity, characterized by multiple clinical symptoms, with typical and/or atypical signs. CHIKV infection can be broken down into three phases, including the acute (the first 21st days following the onset of clinical symptoms), post-acute (from the 3rd week till the end of the 3rd month) and chronic phase (3 months following the onset of clinical symptoms) [1]. Therefore, chikungunya can present diverse clinical symptoms, for which 3–25% of infected individuals are asymptomatic (**Figure 2**) [18]. During the symptomatic phase, the majority of infected patients (90–95%) develop long lasting clinical symptoms coinciding with viremia peak (Elevated viral load ranging between 10^5 and 10^{12} viruses per milliliter of blood) and manifested as debilitating polyarthralgia, myalgia and arthralgia which are rarely fatal (1 in 1000) and not observed in dengue fever [18–20]. Atypical cases of CHIKV occur less frequently and mainly affect elderly, immunocompromised individuals and neonates from viremic mothers [1, 18]. The clinical manifestations associated with these atypical cases include severe neurological dysfunctions (Encephalitis), ocular changes, cardiovascular defect, preterm birth, hyperpigmentation, bullous dermatosis and Guillain-Barré syndrome [1, 18].

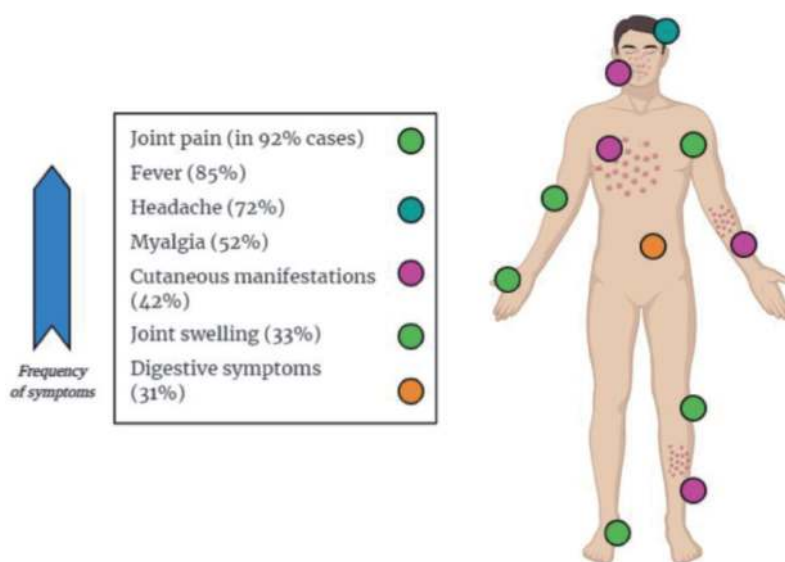


Figure 2. Acute CHIKV clinical symptoms: During the symptomatic phase, CHIKV reportedly causes self-limited fever, as well as debilitating polyarthralgia in most (85–92%) infected patients [18–20]. Also, CHIKV can manifest atypical dermatological symptoms (42%) including edema, hemorrhagic bullous skin lesions, hyperpigmentation [21] and neurological symptoms, characterized by encephalopathy, encephalitis, Guillain-Barré or encephalomyelora-diculitis [22].

Yet, the mechanisms contributing to the long-lasting clinical symptoms remain elusive. An attempt to elucidate this mechanism was made by Reddy et al., 2017, demonstrating CHIKV's ability to evade host immunity as a result of CHIKV E1 glycoprotein homology to the host human counterpart [23]. Consequently, a more detailed understanding of CHIKV replication and infectious cycle is necessary to mitigate these undesired effects.

4. Chikungunya virus genome structure and infectious cycle

CHIKV is a small enveloped virus with a positive single-strand RNA virus belonging to the *Alphavirus* genus from the *Togaviridae* family [1, 21]. It is also referred to as an arbovirus (for *arthropod-borne virus*) due to arthropods transmission (*Aedes* mosquitoes) [21]. CHIKV has an RNA genome of approximately 11.8 kb, comprising two open reading frames (ORFs), known as 5'capped ORF (7424 nucleotides) and 3'polyadenylated ORF (3732 nucleotides), linked by a junction region [22]. The 5'end is protected by a 7-methylguanosine (7MG) cap, with the ORF accounting for 66% of the genome encoding a precursor protein, which upon processing produces four nonstructural proteins (nsP1–4) responsible for CHIKV replication in host cell cytoplasm upon entry [1, 22]. On the other hand, the 3'ORF ends with a polyadenylation signal (3'poly-A tail) and encodes another precursor protein, generating five structural polyprotein comprising: the capsid C, envelop glycoproteins (E1, E2 and E3) and the 6 K protein [1, 22]. **Figure 3A** give a graphic representation of CHIKV genome. Once matured (after replicating in host cells), the virion particle has about 70 nm diameter and possesses 240 copies of capsid proteins embedded in 80 spikes of envelope trimers (glycoproteins E2/E1), which are inserted within the plasma membrane of the infected cells (to evade host immunity) that they use to bud out of the host cells through a secretory pathway [1, 22] (**Figure 3B**). Therefore, elucidating CHIKV replication cycle in both mammalian and mosquito cells becomes pertinent to develop efficient therapies.

CHIKV primarily replicates in the epithelial cells of mosquito midgut before migrating into the salivary glands where they keep replicating throughout the insect life, prior dissemination into the bloodstream of mammalian host, following mosquito bite/blood meal [1, 25]. Once deposited in the human bloodstream or skin after an infected mosquito bite (or blood meal), CHIKV firstly replicates within fibroblasts and macrophages found at the site of inoculation [16]. Thereafter, CHIKV systemically propagates within the body through the lymphatic system to multiple replication sites, where prominent disease symptoms occur (lymph nodes, spleen, skin, muscles, peripheral joints, brain, liver and tendons) despite innate immunity [16]. Notably, CHIKV replication in peripheral tissues is associated with elevated viral loads ($>10^9$ virus particles/ml), which is conducive for mosquito transmission during episodic bloodmeal or bite [16, 26]. Moreover, CHIKV can be transmitted to humans in various ways, including infected needles, contaminated blood donation, organ graft and from viremic mother to newborn [1, 27]. In this regard, Campos et al., 2017 study primarily highlighted the presence of CHIKV in the breast milk of an infected mother, who tested positive for serum and urine [28]. Fortunately, this study did not reveal a breastfeeding transmission capacity of the infected breast milk, as the 3-month-old newborn CHIKV serology and reverse transcriptase-polymerase chain reaction (RT-PCR) tested negative [1, 28]. In light of the latter results, it is worth mentioning that only the structural proteins (surface glycoproteins E2 and E1) are present on the outer surface of CHIKV envelop and are endowed with antigenic potential, able to elicit activation of host immune defense mechanisms [10].

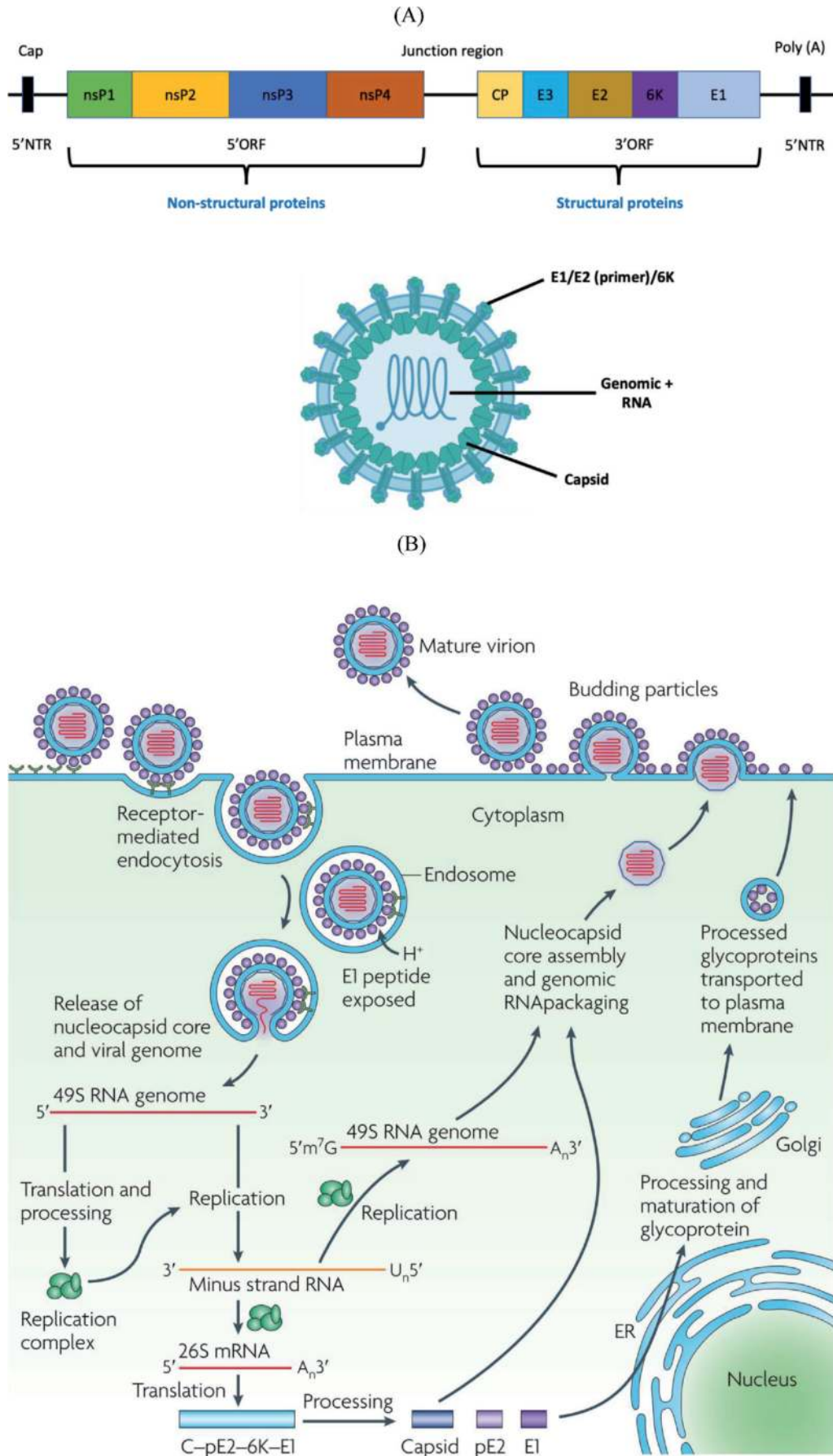


Figure 3.

Chikungunya virus genome structure and infectious cycle. (A) Chikungunya genome structure, (B) chikungunya (CHIK) internalizes within the target cell through receptor mediated endocytosis. Upon entry, CHIK undergo conformational changes leading to E1 peptide exposure as a result of endosomal microenvironment acidity, which favors virus–host cell membrane fusion and subsequent cytoplasmic release of nucleocapsid core and viral genome. Thereafter, two viral mRNA strands are translated to give to two non-structural proteins (nsPs), which are cleaved to generate nsP1–nsP4. The function of the latter are as followed: 1) nsP1 synthesis the negative viral strand RNA and cap it, 2) nsP2 exhibits RNA triphosphatase, helicase and proteinase functions contributing to host cell transcriptional machinery inhibition, 3) nsP3 forms part of the replicase unit and 4) nsP4 exert viral RNA polymerase function. The coordinated activity of these proteins is to produce the viral replication complex, enabling the synthesis of the full-length negative-strand RNA intermediate serving as the precursor to generate the subgenomic (26S) and genomic (49S) RNAs. Once synthesized, the 26S mRNA is translated into C–pE2–6 K–E1 polyprotein precursors, which are further processed by a serine protease to produce a capsid (C), pE2 and E1 glycoproteins. Then, pE2 and E1 assemble in the Golgi and translocate to the plasma membrane, where pE2 is cleaved into E2 (enabling receptor binding) and E3 (ensuring correct pE2 folding and its subsequent assembly with E1). Completion of this viral replication cycle is achieved through 1) assembly of the viral nucleocapsid with the viral RNA, 2) recruitment of membrane-associated envelope glycoproteins and 3) budding at the virus at the host cell membrane [24].

5. CHIKV induced immune response

5.1 The role of innate immunity in chikungunya infection management

The innate immune system refers to the first non-physical and non-specific defense mechanisms to encounter invading pathogens or foreign elements immediately or hours following the appearance of their antigens within the body [29]. To perform its protective role, the host innate immunity relies on antigen-presenting cells (APC) such as macrophages (Mc) and dendritic cells (DC) to neutralize foreign antigens and subsequently present it in a specific way to specialized lymphocytes B (antibody producing cells) and T-cells of the adaptive immunity in secondary lymphoid organs (spleen and ganglions) [30, 31]. Conventionally, all APCs are endowed with the ability to capture an antigen originating from extracellular or intracellular milieu and present it to CD4+ or CD8+ T cells, using major histocompatibility complex II (MHC-II) or I (MHC I) associated peptides respectively [30–32]. However, DCs are endowed with the unique potency to prime CD4+ and CD8+ T-cells (in secondary lymphoid organs) due to their ability to cross-present captured foreign antigens using MHC-II/I complexes [32–34]. Under normal conditions, DC cells exist in immature and inactivated states, hence acting as the sentinel of the immune system [31, 34, 35]. However, DCs are activated into a mature state once exposed to the antigenic determinant of the foreign organism. This DC protective role was illustrated by Long et al., 2013 reporting increased DCs presence at CHIKV infection site 24 and 36 h post infection [36]. Additionally, the latter report highlighted that mice harboring DCs deficiency for dendritic immunogenic receptor (DCIR) displayed more severe CHIKV related symptoms (increased inflammation, edema, weight loss and damage of inoculated foot and the ankle joint) than wild type control [36]. In this line, Das et al., 2015, demonstrated an increase in CD206+ DCs mobilization at the CHIKV infected astrocytes site [37].

Nevertheless, it is well documented that innate immunity following viral infection can recruit inflammatory cells to infected musculoskeletal tissues, with the potential to cause muscular and articular damages inducing the observed pain and discomfort in muscles, joints, and tendons [16]. This CHIKV dependent polyarthritis-like symptoms were reported by Amdekar et al., 2017, to be linked with host inflammatory response regulated by infiltrating macrophages (in joints), T cells, and viral persistence within the immune inaccessible infected sites [38]. Similarly, numerous studies have demonstrated the dichotomic CHIKV reservoir (during chronic infection phase) and modulatory macrophage functions (keeping

local Th1/Th2 balance) in the affected tissues (muscles, joints, lymphoid tissues and liver) that they co-infiltrated with mononuclear inflammatory cells [39–41]. These aforementioned results corroborated Gardner et al., 2010 study, revealing the equally important role of macrophages in establishing arthritis symptoms and CHIKV clearance [42]. Furthermore, Phuklia et al., 2013 and Schett, 2007 showed that CHIKV-infected synoviocytes (Cells producing the synovial fluid component important for absorption from the joint cavity and for synovial/blood fluid exchange) were able to promote the migration and differentiation of both monocytes and macrophages into joints damaging osteoclast-like cells, capable of producing high levels of arthritis mediators (Interleukin-6 and Tumor Necrosis Factor- α) [43, 44]. In contrast, Haist et al., 2017, underlined the protective role of inflammatory Ly6C^{hi} CCR2⁺ monocytes in controlling CHIKV infectious, as their depletion (using diphtheria toxin on CCR2-DTR⁺ mice) was associated with severe disease symptoms and reduction in Ly6C and NK cells in bloodstream and muscles when compared to wild type mice [45].

6. Chikungunya and adaptive immunity

Humoral and cell-mediated immunity hold the center stage for protection against CHIKV infection through the combined action of T and B-lymphocytes, respectively [46]. Multiple human and animal studies have demonstrated the host immune system's ability to induce the production of neutralizing anti-CHIKV antibodies, to rapidly clear CHIKV viral loads and establish long-term immunity [1, 10, 46]. This adaptive humoral immunity relies on immunoglobulin-M (IgM: representing ~30% of circulating antibodies) to primarily entrap the CHIKV antigen to secondary lymphoid tissues by bridging the innate and adaptive immunity before the onset of the robust and specific life-long protecting IgG response [1, 47]. During the chikungunya fever acute phase, neutralizing IgM are produced as early as 2–6 days post-infection and act to reduce viral loads (**Figure 4**) [48]. This neutralizing IgM capacity perdures up to 10 days following CHIKV infection before synergizing with specific IgG response [1]. Interestingly, Couderc and Lecuit et al., 2015 reported persistent anti-CHIKV IgM in chronic chikungunya fever patients related to repeated CHIKV antigen and RNA exposure [49]. Of late, Tanabe et al., 2018 showed that IgM antibodies preferentially interact with cognate E1-E2 fusion glycoprotein epitopes found on CHIKV outer surface [23, 46] and that long term viral immune protection was achieved through specific IgG production, persisting up to 19 years following the first infectious episode (1991 Thailand CHIKV outbreak) [50]. Among all IgG subtypes, IgG3 was found to be the most predominant, able to serve as a predictive marker of high-risk patients (when minimally produced) or as a prophylactic agent, able to passively transfer from mother to newborn via the placenta and limit viral metastases to distant muscles and joints [1]. This pentameric immunoglobulin structure armed them with the ability to easily mediate CHIKV aggregation, recognition and elimination by cytotoxic CD8⁺ T cells [46]. Unfortunately, CD4⁺ T-cells can be detrimental to CHIKV infected mice, as it was reported by Theo et al., 2017 that they can severely damage the joints of T-cell receptor-deficient mice when adoptively transferred [46, 51]. Mitigation of these undesired CD4⁺ T-cell effects could be performed using fingolimod (phosphorylated sphingosine 1-phosphate receptor 1 agonist: S1PR1) treatment, blocking S1PR1 mediated CD4⁺ T-cells dissemination to the joints of CHIKV infected mice [46, 51]. In a parallel study, Miner et al., 2017 demonstrated the synergy of immunosuppressive cytotoxic T-lymphocyte-antigen-4 (CTLA-4) abatacept (blocking CD4 co-stimulatory activating signals) with anti-CHIKV (reducing viral load) in controlling arthritis and CHIKV infection, respectively [52]. This result was

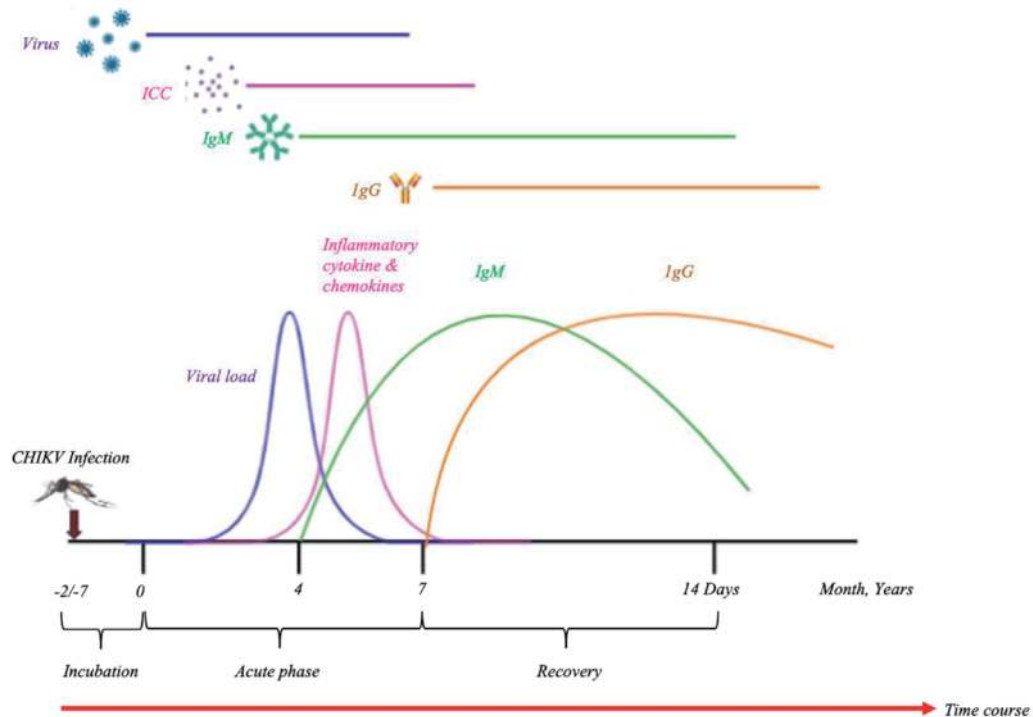


Figure 4. CHIKV infection and immune response: CHIKV infection begin with mosquito's bites, allowing viral entry into serum and subsequent dissemination into peripheral organs (lymphoid, muscles and joints), leading to the onset of symptoms (acute phase) that can perdure beyond 8 days. During the acute phase (0–4 days), neutralizing IgMs are produced, and their increase inversely correlates with CHIKV viral loads. During the recovery phase or convalescence (beyond 7 days), IgGs are produced and act in concert with IgM to provide long-term immune protection.

particularly relevant, as it may pave the way for novel antibody therapeutic strategies, with the potential to clinically benefit CHIKV infected patients.

7. Chikungunya virus therapeutic treatment and future perspectives

Targeted antibody-based immunotherapy was developed to address the unmet CHIKV therapeutic clinical needs [1]. In this regard, immunotherapy using IgG has widely been developed and has demonstrated the potential to reach clinical fruition by exerting its virucidal (Virus killing activity) and prophylactic activities on infected patients [1]. This IgG virucidal effect was confirmed by Scott et al., 2017 showing its ability to induce complete recovery in encephalitis infected patients, using a therapeutic dose of 400 mg/kg for 5 days [2]. With this in mind, Fernandes et al., 2019 corroborated these latter results, by achieving a 10 day total recovery, following a combination therapy involving antibiotic and IgG treatment (400 mg/kg for 5 days) on a severely infected 56 years old patient, presenting with atypical dermatological form associated with edema and hemorrhagic bullous skin lesions [53]. This IgG immunotherapeutic agent could either be used to immunized healthy or asymptomatic individuals in endemic areas (with the aim to reduce CHIKV propagation) or to treat high-risk patients such as pregnant women, newborns, immunocompromised individuals, elders or patients with preexisting arthritis [1]. For example, Couderc et al. 2009 demonstrated the therapeutic and prophylactic actions of IgGs (purified from convalescent CHIKV infected donor), protecting adult immunocompromised and immunocompetent mice neonates from CHIKV

re-challenge and severe neurological symptoms associated with chronic CHIKV infection [54]. Based on these accumulative reports, a phase I/II clinical trial was initiated to evaluate the therapeutic and prophylactic efficacy of CHIKV IgG therapy to newborns of mothers with acute CHIKV infection, whose infectious rates reached 49% (Clinical trials: NCT02230163) [14]. However, the efficacy of CHIKV IgG immunotherapy can be compromised by immune evasion, arising from monoclonal Abs (mAbs) selective pressure or accumulated genetic mutations able to suppress antigen specificity, thus antigen-antibody interaction [1]. With the advent of recombinant antibody engineering technology, efforts to overcome these unwanted effects were developed and led to the generation of bispecific antibodies that can recognize two or more epitopes; a detailed discussion beyond the scope of this review has been provided by Nyakatura et al., 2017 [55]. Besides immune evasion, other factors like antibody-dependent enhancement (ADE), characterized by sub-neutralizing Abs concentration that is permissive for viral replication, has been identified as a major challenge for CHIKV management [1, 56]. In spite of the single serotype status of CHIKV, ADE cannot be overlooked with respect to CHIKV reemergence, as it has been observed in other viral diseases, including Dengue, Rabies virus, influenza and HIV [1]. Also, antibody-based therapy is generally associated with high production costs, which may restrain therapeutic usage due to affordability. To address these issues, nucleic acid vaccines made up of mRNA or

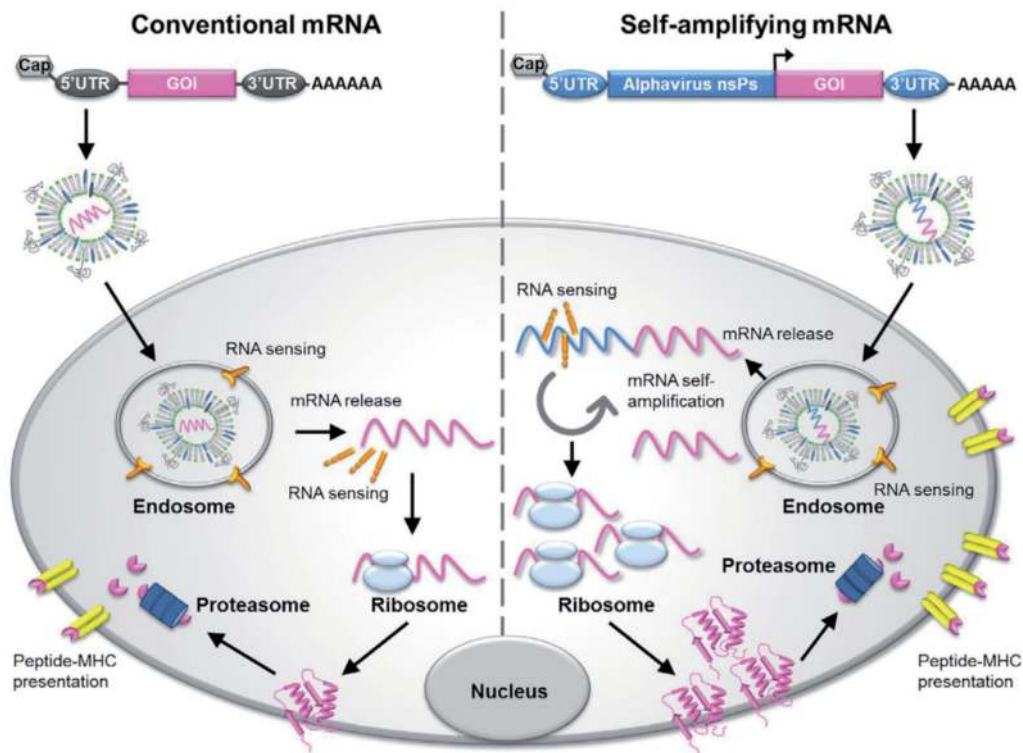


Figure 5. mRNA vaccine mechanism of action. Conventional mRNA possesses disease specific gene of interest (GOI) encoding the antigen DNA sequence that is respectively capped at the 5' end and polyadenylated (poly-a tail) at the 3' untranslated region (UTR). Upon internalization within the host cell, viral mRNA is released from the endosome to the cytosol, where it is immediately translated by the ribosomes and post-translationally modified by the proteasome. In opposition to the conventional mRNA vaccination, the self-amplifying mRNA method mostly uses positive-sense single-stranded viral RNA encoding the disease specific antigen and viral nonstructural proteins (nsPs) driving intracellular RNA amplification and significant antigen expression. These two vaccination methods need a delivery system for host cell internalization, commonly performed through endocytosis, preceding cytosolic viral mRNA cargo releases from the endosome, driving translation and subsequent viral antigen protein processing for MHC presentation to ensue and activate host immunity [59].

plasmid DNA (pDNA) were developed [57, 58]. These novel vaccines are commonly used to treat mRNA alphavirus and are mainly produced by genetically substituting viral encoding structural protein with target antigen encoding genes while preserving the RNA replication machinery [57]. Hence, when injected into patients, these vaccines (mRNA) mimic the virus by taking advantage of the host cell machinery to efficiently transcribe an antigen encoded RNA into an antigen encoded DNA, which is subsequently translated and post-translationally modified into a form (protein) that resemble the natural antigen that can successively stimulate and activate the innate and adaptive immunity (**Figure 5**) [57, 58]. Recently, Kose et al. (2019) demonstrated CHIKV and arthritis protecting properties of an infused nanoparticle encoding CHIKV antibody mRNA, which was as good as purified IgG mAbs in stimulating protective anti-CHIKV serum concentrations in macaques [60].

So far, there are no clinically approved RNA vaccines to treat human diseases. Yet, in response to the ongoing coronavirus disease 2019 (COVID-19) pandemic, multiple clinical trials such as NCT04283461, have been initiated to test the safety of an mRNA vaccine (encoding SARS-CoV-2 spike protein), which successfully produced SARS-CoV-2 antibodies and had no clinically adverse effects [61, 62]. Currently, it has progressed into phase III clinical trial (NCT04470427) to evaluate its efficacy against COVID-19. Likewise, other clinical trials are presently investigating the safety, tolerability and immunogenicity of zika virus envelop protein encoded mRNA vaccines (NCT04064905; NCT03014089) [61, 63]. Taken altogether, it becomes evident that the rapid advances made in recombinant DNA technology, will revolutionize the way we approach and promptly respond to endemic CHIKV/COVID-19 like diseases.

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