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Review Article

Chikungunya Virus (CHIKV) Infection and the Protective Immunity: A Narrative Review

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Abstract

Chikungunya virus (CHIKV) has been well known for causing the epidemic disease outbreaks mainly streaming into inflammations like the severe joint pains. Re-emergence of chikungunya viruses around the world is one of the most important clinical issues. Like the dengue viruses (DENV), CHIKV can initiate the systemic infection caused by the vector Aedes mosquito bites. Propagation of the viral elements principally appears to cause arthralgia in a similar pattern like DENV- or Zika virus (ZIKV) infections. Like DENV infections, the morbidity and mortality rate due to CHIKV infection may be intense especially among the older people. Components of the innate immune system like the type I interferon along with the CHIKV specific immunoglobulins are known to impart enduring immunity to CHIKV while they may also exert the immunopathologic role in the CHIKV pathogenesis. Indeed, the infection with CHIKV triggers the release of an array of cytokines and chemokines which in turn generate anti-viral response. Current review further pointed on the immune strategies exerted by the hosts against the CHIKV elements. Besides, the generation of both the innate immunity and the adaptive immunity at the early- and late stage of CHIKV infections is discussed together with the presentation of new models.

Keywords: *Re-Emerging Infection; Chikungunya Virus (CHIKV); Immunity; Anti-Viral Response*

Introduction

Infection by chikungunya viruses (CHIKV, belonging to the *Togaviridae* family), caused by the mosquito bites (*Aedes aegypti* and *A. albopictus*) has spread in many parts of the world over the last 70 years [1-4]. While bats and rodents are the occasional reservoirs; the mosquito *Aedes aegypti* serves both as the principal vector and the reservoir for transmission of CHIKV [5]. Indeed, after *A. aegypti* (the daytime biting mosquito, usually staying within the indoor stagnant waters) transmits CHIKV into the human hosts; the mosquito can serve as the reservoir too. Such continuous cycle of the human-mosquito-human transmission is very much likely to spread to the adjacent areas [6]. On the contrary, *Aedes albopictus* (known as the late afternoon biting mosquito) usually stays outdoor [7,8]. An investigation on *Ae. albopictus* females in Yaoundé, Cameroon, Central Africa showed that the human-biting activity of female *Ae. albopictus* raised highest in the late afternoon [8].

The outcome of the infection is mainly characterized by arthralgiasis, the peripheral joint pains and the muscle aches resembling the same as happens during the primary infections caused by the dengue viruses (DENV) [1,9-12]. Interestingly, CHIKV- and the zika virus

(ZIKV) co-infections have been noticed in some instances which really urges for a detailed study on the genetics and immunology of these viral infections for the sake of a clear understanding of the disease pathogenesis which in turn would go a long way to maintain a sound global public health [13]. The CHIKV genome is known to be a positive sense single strand RNA (49S) consisting of 11811 nucleotides, encoding the non structural proteins (responsible for the viral replication), structural proteins (aiding in new particle synthesis) and the small peptide [13-16]. After getting entry into the hosts' blood streams, the CHIKVs adhere to the monocytes and start replication until the progeny viruses are released into the targeted organs including the joints, lymph nodes, kidney, and even to brain [17]. Eventually, after the translation of both the non structural and the structural proteins, new CHIKV particles are released [18,19]. Indeed, upon entry of the RNA component of the CHIKV into the cytoplasm, the primary translation occurs yielding a polyprotein consisting of replicase which in turn facilitates the synthesis of the new and complete RNA at the early replication stage of CHIKV genome [19].

The extent of CHIKV infection is simply worldwide. To date it's very well known that the CHIKV was introduced into Asia from Africa. The first case of chikungunya encounter was reported in Tanzania in 1952; and for about half a century the sporadic cases conquered Africa. Then the fever re-emerged starting from Kenya (2004), Indian Ocean islands (2005), Cameron (2006), Gabon (2007), Sri Lanka (2008), India and Singapore (2009), Franceville (2010); and finally to Bangladesh (2008) [20-24]. According to the reports of icddr,b (International Centre for Diarrhoeal Disease Research, Bangladesh) and IECDR (Epidemiology, Disease Control and Research), in Bangladesh, the first attack by CHIKV (over 30 cases) took place in its south-western part in 2008, followed by the second outbreak in the north-western zone of the country in 2008; and in 2011, nearly 4000 people were found to be affected by CHIKV infection [20,21]. In 2017, more than CHIKV infection 3000 cases were reported [22].

For the developing countries like Bangladesh where the immunological knowledge as well as the prompt diagnosis is not that up to mark, it's really important to raise the public awareness on the fatality of CHIKV as well pondering towards the reasons and the associated remedies. Resisting the growth of *Aedes* mosquito through regular drainage of the stored waters, usage of anti-*Aedes* chemicals, etc. would be of important issue in these countries. However, for the health professionals the extensive knowledge on the protective immunity is stringently required which must be simply communicated for establishing the required legislative bodies in the local sectors; for the regular monitoring of the infected cases; and for maintaining the sound level of public health. Besides CHIKV infection, this year (in 2019) the DENV infection frequency also increased drastically caused by the same arthropod vector mosquito [10]. Unfortunately, the chemotherapy based protection against chikungunya has not been established yet since there are no accredited vaccines or antivirals against CHIKV although certain trials are under development (i.e. in the pre-clinical trials) using the live-attenuated- and the inactivated viral vaccines, the recombinant viral- and the DNA vaccines, the chimeric-alphavirus candidates; and the virus-like particles (VLPs)- vaccines [23]. Moreover, the rate of CHIKV (the re-emergence) round the globe is quite frequent together with its expanding geographic range [24,25]. The host innate response and the adaptive immune response against CHIKV have been well analyzed from the point of both imparting the protection and towards the contribution to the virus-mediated immune pathology [26-28]. Therefore, it's worth to analyze the immune cells which can come up during such viral infections.

Indeed the incidence of gathering of type 1 IFN-γ from the innate immune system has been evidently reported as a protective strategy by the CHIKV-infected individual as well as the blast of CHIKV specific immunoglobulins have also been detected with the milieu of long-term immunity [13]. Combining the significant immunological studies so far conducted on chikungunya, current review, therefore, principally focused on the spatial roles of the components of the immune systems (macrophages, dendritic cells, monocytes, different cytokines and chemokines, B cells, T cells, etc.) upon the infection with CHIKV particles with a precise discussion both at the early- and late stages of infection along with the innate and the adaptive immune responses.

Specific impacts of CHIKV infection

The impacts of CHIKV infection among the neonates, infants, children and adults are well known along with its fatality within the individuals aged more than 60 [28]. As stated earlier, the CHIKV particles have been noticed to replicate within the skin followed by fur-

ther dissemination into the liver, muscle, joints, lymphoid tissue and brain [29]. However, CHIKV has been largely been known to spread through the blood stream following infection of the joints within the body leading to bone weakening followed by the eventual damage, rheumatoid arthritis, enhanced osteoclastogenesis, and polyarthralgia [23,30]. Both CHIKV and ZIKV have been reported to manifest intraocular inflammation including conjunctivitis, retinitis, tearing, blurred vision, chills, photophobia, corneal edema, irritation, etc. [26,31,32]. It is to be noted that the chikungunya viral disease (CHIKVD) can be extremely lethal mostly in individuals with pre-existing diabetes and cardiovascular disorders [23].

Besides, CHIKV is also known to be one of the principal causes of miscarriage during the early stage of the pregnancy [33]. Another dreadful point to be pondered is that CHIKV can be detected even in the breast milk which can be transmitted to the infants [34]. Indeed, CHIKV infection can lead to mortality especially due to faulty medication as reported by several case studies [15,30,33,34]. Therefore, the early diagnosis of CKIKV is important which is commonly known to be based on serology (detection of the high titer of IgM) [35]. Indeed, the symptoms of arthralgia have made the CHIKV infection unique; that is distinguishable from DENV infection. It's also interesting to note that most mammals and a smaller proportion of birds have been found to develop neutralizing antibody responses against CHIKV which in turn may reflect that CHIKV may not pose a momentous health risk to most familial animals [5].

Protection against CHIKV: immunological basis

As in the cases of other disease mitigation, the protection against CHIKV infection should principally depend on the regular anaphylactic drugs as well as on the antivirals. Some anti-virals including favipiravir (T-705), harringtonine, nucleoside analogue β-D-N^4-hydroxycytidine (NHC), engineered mAb mimicking the neutralizing anti-CHIKV human mAb 4N12, the combined therapy with CTLA4-Ig and the 4N12 mAb are still being analyzed in the *in vitro* scale and not *in vivo* for their efficacy [23]. While researchers have been trying to develop the effective vaccination against CHIKV, the epidemic of the disease is getting expanded unfortunately due to the active products. Therefore, it's really important to understand the molecular mechanism underlying the CHIKV infection which in turn may trigger the CHIKV pathogenesis as in DENV [10].

The phenomenon of the long-term immunity against CHIKV re-infection has already been known to quite a large extent ranging across the CHIKV genotypes from the epidemiological observations so far [27,29]. Indeed, CHIKV infection is usually starts after the mosquito bite which actually triggers the replication of the viral particles. CHIKV progeny elements then spread into the peripheral organs: i.e. muscles, dermis, joint connective tissue, lymph nodes, spleen, liver and the central nervous system (CNS) via the circulatory system (blood stream) and directed to the target cells including the macrophages. Eventually both the innate- and the adaptive immunity are evoked (Figure 1). Innate immunity involves the dendritic cells (DC), macrophages, the activated subpopulation of monocyte $CD14^+$-driven response especially in case of the acute infection [36]. Besides, the function of the natural killer (NK) cells is known be controlled by a combination of signals from activating receptors like NKG2A along with the inhibitory killer cell immunoglobulin-like receptors (KIRs) on their cell membranes [37,38]. However, this is to be pondered that the accurate function of the natural killer-like cells (NK $CD3^-CD56^+$) in CHIKV disease progression or recovery still remains obscure [38].

The $CD14^+$ monocytes are engaged in activating the B- and T-lymphocytes and hence thereby initiating the adaptive immunity which is apparently understood by the dominance of immunoglobulin G3 (IgG3) antibodies (Figure 1). Infected individuals with high viremia at the early stage have been reported to possess the elevated levels of IgG3 [39]. At the early stage of infection, the T cell subsets; i.e. both $CD4^+$ T cells and the cytolytic CD8 T^+ cells, trigger the production of various cytokines including an array of interferons and interleukins (Figure 1 and 2) which in turn augment the cell mediated immunity as well as the antibody response along with the association of the cytotoxic T-lymphocyte-associated protein 4 (CTLA4).

As shown in figure 2, one important thing is to ponder that the production of cytokines IL-1β, IL-8, and chemokines including the RANTES (the C-C motif ligand 5, the chemotactic for T cells, eosinophils, and basophils; recruiting leukocytes into the inflammatory sites;

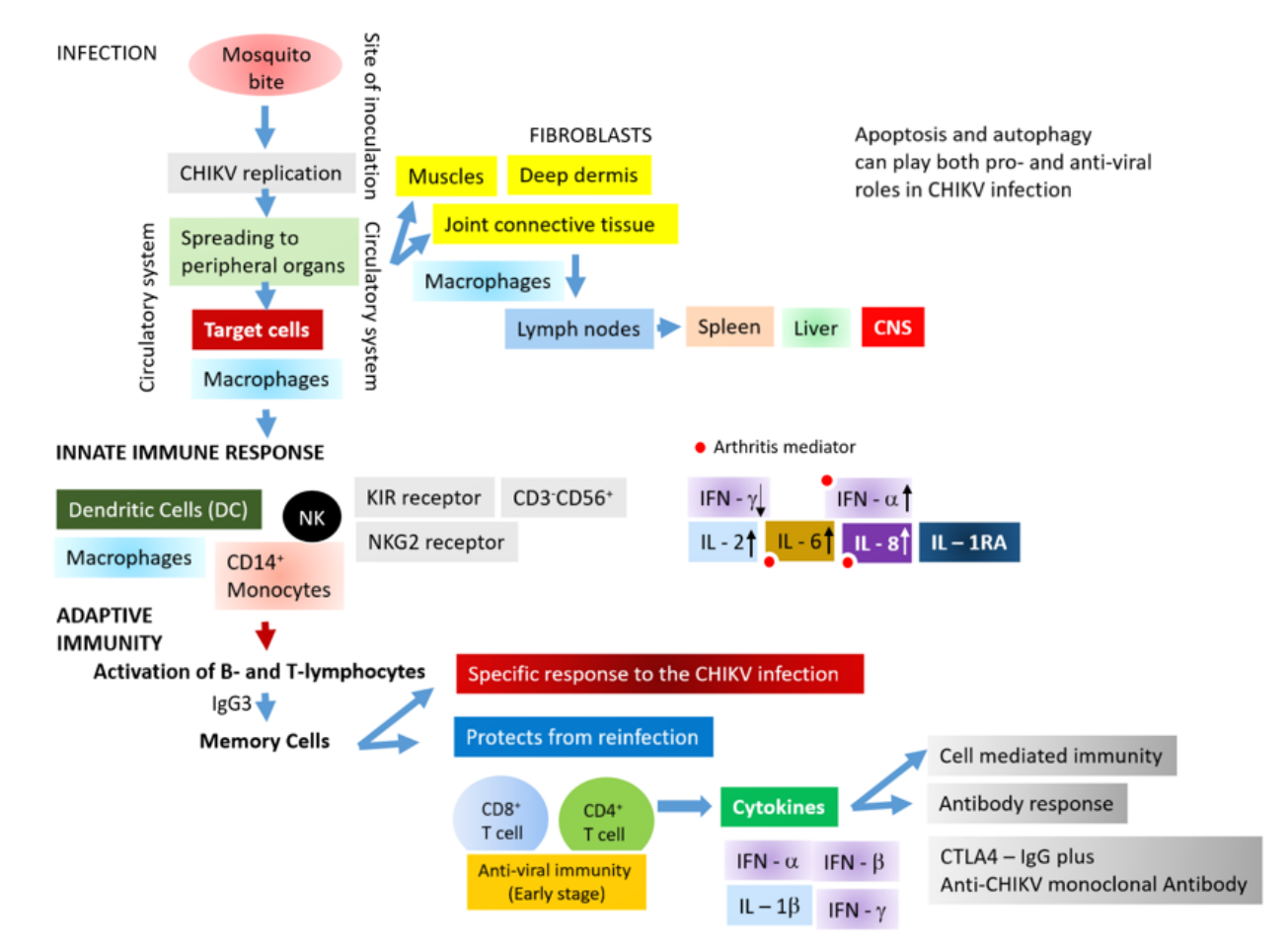

Figure 1: *Onset of innate immunity and the adaptive immunity upon chikungunya virus (CHIKV) infection. Following infection CHIKV elements disseminate into the peripheral organs via the circulatory system and directed to the target cells together with macrophages. As a result, both the innate and the adaptive immunity are triggered. Dendritic cells (DC), macrophages, and the monocyte CD14⁺ cells are involved in the innate immunity while the CD14⁺ monocytes are involved in the activation of B- and T-lymphocytes, resulting in the IgG3 blast.*

and inducing the blast of NK cells) levels during acute CHIKV infection can be regarded as the biomarkers of Chikungunya which in turn can enable the precise diagnosis and monitoring of the infected patients [40]. The role of the monocyte chemoattractant protein 1 (MCP1) is nearly similar to that of RANTES. The cytotoxic lymphocyte maturation factor p40, also known as the interleukin-12 subunit p40 (IL-12p40) may also mediate long-term protection against the CHIKV infection [39.40].

In summary, the infection with CHIKV pauses the host cell translation which in turn results in the release of cytokines and chemokines including β- interferon (IFN), interleukin (IL) 4, IL-6 and IL-10 that are supposed to work in an orchestrated way to generate anti-viral activities [41,42]. Besides, the IL-signals help the natural killer (NK) cells to identify the CHIKV infected cells so that those can be destroyed

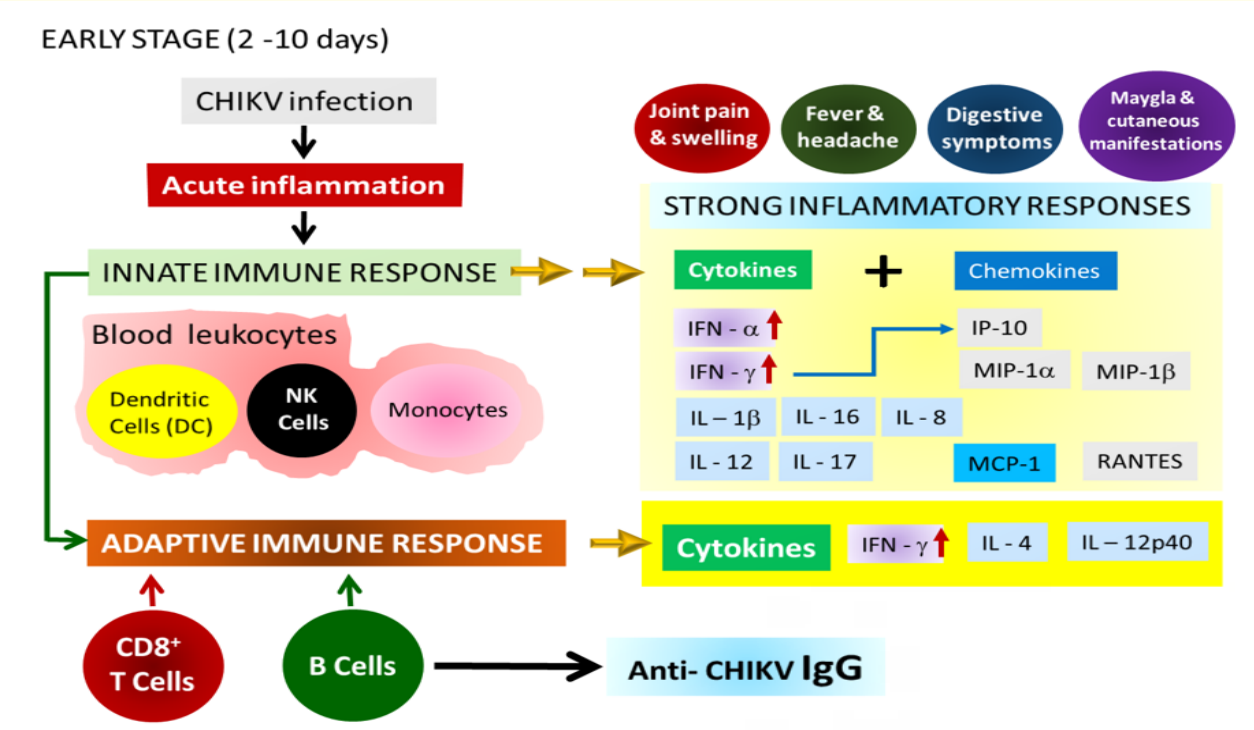

Figure 2: *Outcome of CHIKV infection at the early stage. As outlined in figure 1, at the early stage (during 2-10 days) the infections may be acute and both the innate and adaptive immune responses are triggered. Besides the production of the cytokines and chemokines, the innate immune response may be characterized by the strong inflammatory responses like joint pains, fever, headache, indigestion, maygla, etc. The high concentrations of IFN-α and IFN-γ may induce the production of IP-10 (chemo attractant for the monocytes, macrophages, T cells, NK cells and the dendrites), the macrophage inflammatory proteins, MIP-1-α and MIP-1β. The most significant event to note is the production of the anti-CHIKV antibody mediate by the adaptive immune response.*

by the cytotoxic effects by the Th_1 cytokines which are known to activate the $CD8^+$ T cells during the early stages of CHIKV infection [43,44]. In the late stage of the infection, both the $CD8^+$ T cells and $CD4^+$ T cells can be activated to adhere with the MHC class II molecule on the antigen presenting cells, APCs [45]. Eventually the $CD4^+$ T cells activate both B lymphocytes (producing immunoglobulins) and also the T lymphocytes. Besides, as shown in figure 3, the levels of cytokines including the IFN-α, IL-1RA, IL-6, IL-7, IL-8, IL-12, and IL-15 have been reported to increase significantly [46-49]. In addition to the findings from the previous literature, the current review further pondered to the systemic spread of the CHIKV across the peripheral organs of the hosts upon infection accompanied with the activation of the components of the immune systems including the dendrites, macrophages, monocytes which are essentially involved in triggering the protective innate immunity and the adaptive immunity as well as with the blast of the immunoglobulin IgG3 in accordance to the early- and late response stage response towards the CHIKV infection (Figure 1-3). The role of antibody in protective immunity is one of the major focuses of the current review. Indeed, previously the inducible immune defensin peptides were characterized through the expression of *defA* and *defC* expression in CHIKV particle [1].

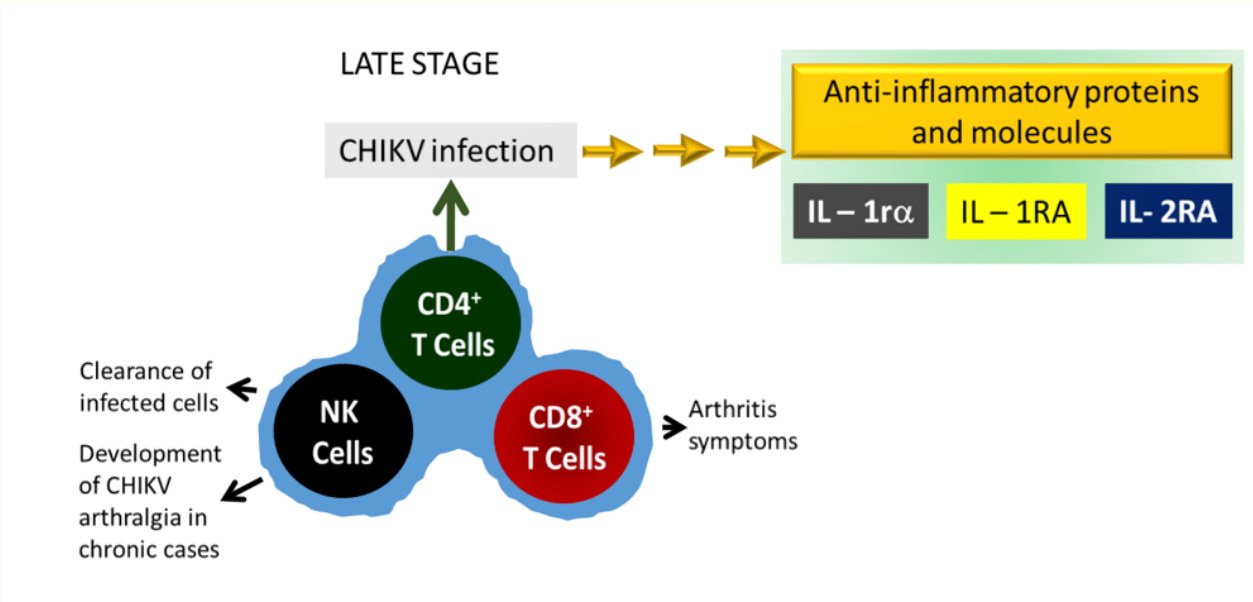

Figure 3: *Production of anti-inflammatory substances during the late stage of CHIKV infection. At the late stage of infection, principally in association of CD4+ T cells, CD8+ T cells, and the NK cell; an elevated level of IL-14α, IL-1RA and IL-2RA (serving as growth factor) is noticed.*

Common remedies

While a number of researches have analyzed the development of vaccines or antivirals against CHIKV infection, in real the outcome is not that satisfactory since the therapeutic development is still under scrutiny especially focusing the drug-target development as well as the CHIKV lifecycle including various stages of infection (entry and replication) [17]. Besides, although a few potential inhibitors like catechin-5-O-gallate, rosmarinic acid and arjungenin for CHIKV particles were identified still the requirements for the *in vitro* studies on such inhibitor-activity have been suggested further [19]. Besides, a couple of years ago, the non-steroid anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs) were suggested for relieving the joint pain and swelling [23].

As stated earlier, CHIKV is an emerging epidemic-prone pathogen imparting similar clinical manifestations to some other mosquito-borne pathogens such as the dengue virus (DENV) which have the nearly similar transmitting vector as well as showing alike geographical distribution of outbreaks, which often may remain undiagnosed [16]. Such incidences of CHIKV infection and co-infections with DENV or with Zika virus have largely drawn the urge for CHIKV infection management. Therefore, CHIKV infection and mass public awareness against CHIKV infection may be brought by resisting the growth of *Aedes* mosquito which is responsible for transmitting arboviruses like ZIKV and CHIKV. As these mosquitoes are responsible for transmitting the virus, they can be killed by applying insecticides, larvicides in the breeding places [50]. As *Aedes* mosquitoes breed on the stagnant water, such places should be aimed for the chemical killing. Containers, flower vase or other places which can store water for several days should be drained or changed daily [50]. At the same time, mosquito biting can be resisted by wearing full sleeve dresses, socks, full pants and applying mosquito repellent cream or spray [20-22,51]. CHIKV infected people should be careful by staying inside the net as much as possible, especially during the biting time of *Aedes* mosquito to stop further biting because the infected person act as the viral reservoir containing a huge load of viral titer which can be easily disseminated to susceptible persons by further mosquito bite [52].

One important fact is to ponder that the only diagnostic strategy in Bangladesh relies on the collection of blood specimens together with recording clinical histories from the self-selected suspected cases followed by the examination for the IgM antibody titer [21]. Thorough investigation of the immune system combating such viral attack is completely absent due to the resource poor settings let alone the investigation through the phylogenetic analysis [29]. Therefore, it is apparently evident that since there is no appropriate treatment and vaccination against CHIKV available in Bangladesh till date, the preventive measures can be the only way to resist the infection spreading further. Moreover, it should be noted that the effectiveness of therapeutic strategies against CHIKV infection as well as the vaccine candidates so far proposed is largely reliant on huge financing; the stability of the research based product and its validation (i.e. the long-term public health measures) [23]. Finally, the maternal transmission of CHIV particles to fetus is not unlikely and that's why it's worth to set up the research facilities on the pathogenesis as well as on the probable mitigation strategies of this virus [33].

Conclusion

Lots of comprehensive reviews have been published about the immune systems working against CHIKV infection with all the details and required knowledge. Present review projected towards the immune responses against CHIKV specifically to communicate the concept of protective immunological strategies against such viral infections. From the discussion and the models plotted in the current review it's now well understood that after the infection with CHIKV, the virus halts the host cell translation which triggers a significant production of IFN-β, IL-4, IL-6 and IL-10. IFN type 1 generates JAK-STAT signaling to the infected cells to produce antiviral proteins to resist further CHIKV infection. The NK cells can detect the CHIKV infected cells by the interleukin signals and destroy them using cytotoxicity. Such an understanding on the CHIKV pathology along with the early- and late stage response of the innate- and adaptive immunity would be of great impact to put forward the current knowledge and the associated research on chikungunya especially for the developing countries where such research is really scarce due to require expertise. In Bangladesh perspective, the research on CHIKV has extensive gaps in the understanding of the molecular mechanism of viral multiplication within the host as well as the protective immunological components which simultaneously work. Therefore, extensive logistic supports are required for the initiation of the detailed understanding of the CHIKV pathogenesis and preventive measures.

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Conflict of Interest

Author has declared that he has no conflict of interest.

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