

Host Response and Mechanisms of Subversion of Chikungunya

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Chikungunya Fever and Disease Manifestation

Chikungunya fever (CHIKF) is an arthropod-borne viral disease transmitted by the *Aedes* mosquitoes, and is characterized by fever, headache, rashes, and debilitating arthralgia (Pialoux et al. 2007; Robinson 1955). Caused by the chikungunya virus (CHIKV), an alphavirus belonging to the *Togaviridae* family, the virus has an incubation period of 3–7 days (Powers and Logue 2007). Although only up to 15 % of asymptomatic cases were reported in patients, CHIKF remains primarily a nonfatal incapacitating disease. However, severe forms including deaths, often associated with comorbidities have been reported in the 2005–2006 Indian Ocean islands outbreaks (Lemant et al. 2008; Mavalankar et al. 2007). Similar clinical manifestations were also described from the new wave of CHIKV outbreaks in the French West Indies and Caribbean islands since November 2013 (Leparc-Goffart et al. 2014). The virus has since spread to several parts of Central and Latin America (Morens and Fauci 2014; Weaver and Lecuit 2015).

Typical disease symptoms in most patients (>85 %) include abrupt febrile illness (temperature usually >38.9 °C), maculopapular rash with articular pains. Other symptoms include myalgia, headache, edema of the extremities, ocular manifestations, and gastrointestinal symptoms (Borgherini et al. 2007; Lakshmi et al. 2008), and may be linked to direct or indirect effects of viral replication in these tissues

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(Ozden et al. 2007). Rheumatic manifestations in up to 50 % of the adult patients (6 months to 1 year PI) typically consisted of a febrile arthritis mainly affecting the extremities (ankles, wrists, phalanges; Borgherini et al. 2008; Brighton and Simson 1984; Fourie and Morrison 1979; Manimunda et al. 2010; Schilte et al. 2013; Simon et al. 2007; Sissoko et al. 2009).

CHIKF is usually benign in children. Atypical manifestations with subsequent sequelae have also been described in newborn babies such as neurological manifestations ranging from simple and complex febrile seizures to meningeal syndrome, acute encephalopathy, diplopia, aphasia, acute disseminated encephalomyelitis, and encephalitis (Le Bomin et al. 2008; Lewthwaite et al. 2009; Robin et al. 2008; Valampampil et al. 2009). Severe skin blistering has also been described with intraepidermal vesiculobullous lesions (Robin et al. 2008; Valampampil et al. 2009). Conversely, persistent arthralgia and exacerbation of underlying medical conditions are rare in children.

Notably, the epidemics in La Réunion were the first evidence with severe adult cases and deaths due to CHIKF (Economopoulou et al. 2009). These cases occurred on underlying medical conditions (cardiovascular, neurological, and respiratory disorders). Furthermore, there was a 22 % increase in adult patients with Guillain-Barré syndrome that required respiratory support during the La Réunion outbreak (Lebrun et al. 2009). This phenomenon was also observed in the 2014–2015 epidemic in French Polynesia (Lastère S unpublished). Taken together, atypical severe clinical manifestations as a result of CHIKV infection accounted for close to 1.5 % of the total infected population (4147 hospitalized out of 266,000 cases in La Réunion; Soumahoro et al. 2011; Renault et al. 2012). Fortunately, acute organ dysfunction comprised less than 0.2 % of the total severe cases (Renault et al. 2012; Cabié et al. 2015).

It is important to note that CHIKV also had profound acute arthritogenic activities in patients over 60 years of age that could have contributed to chronic incapacitating arthritis described in other alphaviral diseases in Australia, South America, and Northern Europe (Harley et al. 2001; Levine et al. 1994; Suhrbier and La Linn 2004; Tesh 1982; Toivanen 2008). Moreover, patients with post-CHIKV rheumatoid arthritis- (RA-) like illnesses were also reported (Chopra et al. 2008). The development of progressive erosive arthritis was also reported in some studies (Brighton and Simson 1984; Malvy et al. 2009; Manimunda et al. 2010). However, in contrast to what is known in canonical autoimmune RA, the levels of RF and anti-CCP antibodies were not elevated (Manimunda et al. 2010), thereby suggesting that post-CHIKV arthritis was a chronic inflammatory erosive arthritis. Nonetheless, the current lack of relevant animal models to study CHIKV-induced chronicity limits the understanding of these rare events.

Infection and Disease Pathogenesis: Human and Animal Models

Cutaneous manifestations that subsided without any sequelae in 3–4 days have been reported (Prashant et al. 2009). This eruption could be a hallmark of the inflammatory response of the skin (the portal of entry of the virus after the mosquito's bite)

that mobilized resident cells such as keratinocytes, melanocytes, and dermal fibroblasts (Couderc et al. 2008; Puiprom et al. 2013). CHIKV has been postulated to interact with resident dendritic cells (DCs) including Langerhans cells that contribute to virus spread to other target organs such as muscles, liver, kidney, heart, and brain (Kam et al. 2009).

In an effort to further understand the mechanisms of CHIKV pathogenesis, animal models have been established in mice and nonhuman primates. Studies on mouse models have been focused mainly on acute pathologies induced by CHIKV and disease severity. Notably, only some wild-type laboratory strains are susceptible to CHIKV infection (Ziegler et al. 2008; Gardner et al. 2010). Regardless of age and inoculation routes, susceptible mice in adult wild-type (Gardner et al. 2010; Teo et al. 2013), and also in newborn and young mice (Couderc et al. 2008; Ziegler et al. 2008; Morrison et al. 2011) develop viremia, and skeletal muscles exhibit severe necrotic myositis and high viral load. Pathological changes are also observed in joint-associated connective tissues adjacent to affected muscles. Although CHIKV RNA is cleared from most tissues within days after infection, viral RNA may persist in joint-associated tissues for at least 16 weeks, associated with histopathological evidence of joint inflammation (Hawman et al. 2013). In the case of severe disease, viremia is high and CHIKV also disseminates to other tissues, including skin and eye. In all these tissues, CHIKV-positive cells were identified as fibroblasts (Ziegler et al. 2008; Couderc et al. 2008). These findings are relevant for human disease, as similar tissue and cell tropisms have been observed in biopsy samples of CHIKV-infected human patients (Couderc et al. 2008, 2012). Together, these data demonstrate that infection of peripheral tissues associated with human CHIKV disease, joints, muscle, and skin, is mainly restricted to conjunctive tissues and that the fibroblast is a predominant target cell of CHIKV during acute CHIKV infection.

In the Cynomolgus macaque (*Macaca fascicularis*) model, both acute and chronic manifestations could be monitored. During acute infection, viremic levels up to 10^8 pfu/ml could be detected in CHIKV-infected macaques (Labadie et al. 2010; Roy et al. 2014; Messaoudi et al. 2013). At day 4 post-infection (pi) CHIKV could be detected in the cerebrospinal fluid of all tested macaques, but clinical neurological disease was detected only in macaques receiving the highest infectious doses (Labadie et al. 2010). Interestingly, the acute infection was tightly controlled given that the viral titer was reduced to basal levels at day 10 pi, similar to reports described in patients or mice (Ziegler et al. 2008). These viral replication profiles were also recorded in rhesus macaques (Akahata et al. 2010; Chen et al. 2010). Similar to patients, early leukopenia was observed (Akahata et al. 2010; Borgherini et al. 2007, 2009; Labadie et al. 2010) together with markers of IFN- α/β antiviral response, inflammation, and cell immune activation (Higgs and Ziegler 2010; Labadie et al. 2010; Messaoudi et al. 2013). Infection in pregnant rhesus macaques did not transmit the virus to the fetus in utero (Chen et al. 2010). Nonetheless, experimental infection of newborn macaques remains to be explored and these studies will be able to confirm the capacity of CHIKV to infect and replicate within immature brain tissues.

Cell Targets and Their Role in Pathogenesis

Both hematopoietic and nonhematopoietic cells have been demonstrated in the control of CHIKV infection by the innate immune system (Her et al. 2010; Schilte et al. 2010). Although nonhematopoietic fibroblasts have been reported to be susceptible to CHIKV replication (Sourisseau et al. 2007), it has been established that primary monocytes and macrophages are the major hematopoietic subsets targeted by CHIKV in virus-induced pathogenesis in both CHIKF patients and in animal models (Her et al. 2010; Hoarau et al. 2010; Labadie et al. 2010; Teng et al. 2012; Gardner et al. 2010). Furthermore, MCP-1 (Romano et al. 1997), a monocyte/macrophage chemoattractant (Lu et al. 1998) was shown to be significantly associated with the acute phase of CHIKV infection both in patients and animals (Chen et al. 2010, 2014; Gardner et al. 2010; Hoarau et al. 2010; Teng et al. 2015). In animal models, the high levels of MCP-1 were accompanied by increased infiltration of monocytes into the site of inflammation (Gardner et al. 2010; Labadie et al. 2010; Poo et al. 2014a), thus allowing newly produced viruses by the fibroblasts to infect monocytes/macrophages. To further support this hypothesis, treatment with MCP-1 inhibitor Bindarit (Bhatia et al. 2005) was demonstrated to abolish CHIKV-induced pathology completely (Rulli et al. 2011; Chen et al. 2014).

In macaques, CHIKV could persist in target tissues after its clearance from the blood, as demonstrated by immunohistochemistry and viral RNA detection using PCR and in situ hybridization assay (Labadie et al. 2010). At 7 or 9 days pi, CHIKV was detectable in nearly every organ or compartment tested: joints, secondary lymphoid organs, and, to a lesser extent, muscles up to 3 months pi. CHIKV was shown to replicate in several cell types during the acute phase (Higgs and Ziegler 2010; Labadie et al. 2010), but thereafter was detected mainly in macrophages by immunohistochemistry. CHIKV-infected monocytes and macrophages could be detected in the blood 6 h after infection (Roques et al. 2011) and in most tissues in the following day (by in situ hybridization, immunohistochemistry, RT-PCR, and virus isolation). Significant macrophage infiltration was also detected by histology throughout the study and long after virus clearance in blood (Labadie et al. 2010). Similarly, CHIKV was demonstrated to infect primary macrophages in vitro (Rinaldo et al. 1975; Sourisseau et al. 2007), resulting in the production of highly variable amounts of virus, from 10^3 to 10^6 pfu per ml (Gardner et al. 2010; Hoarau et al. 2010; Krejbich-Trotot et al. 2011a, b; Labadie et al. 2010; Sourisseau et al. 2007). However, CHIKV infection in CCR2^{-/-} knockout mice resulted in a more severe, prolonged, and erosive arthritis, with no effect on virus replication (Poo et al. 2014a). Loss of CCR2, which is the receptor for MCP-1, caused a drastic change in the profile of infiltrating immune cells, coupled with a dysregulation of both pro- and anti-inflammatory pathways. Altogether, these data support the role of monocytes/macrophages as the cellular vehicle for virus dissemination, as well as a cellular reservoir for persistent CHIKV infection in immune-competent mammals.

Other than the increased infiltration of monocytes/macrophages, NK cells were also observed in large quantities in the inflamed joints of infected mice (Gardner et al. 2010). Furthermore, IL-12, which stimulates NK cell activity (Orange and Biron 1996),

was also present in high quantities, suggesting that activated NK cells play significant roles during CHIKV infection (Nakaya et al. 2012; Teo et al. 2015). Clinically, the role of these cells has been verified in natural CHIKV infection in humans where NK cells from CHIKF patients were strongly activated within the first days post-infection and led to a more sustainable CD4/CD8 response against several viral proteins (Hoarau et al. 2013; Petitdemange et al. 2011; Wauquier et al. 2011).

Separately, osteoblasts have been shown to be infected by CHIKV and drive osteoclastogenesis in vitro (Noret et al. 2012). This was confirmed by patient cohort studies where high levels of RANKL/osteoprotegerin (OPG) detected in CHIKV patients could be associated with macrophage-derived osteoclasts (Her et al. 2012; Chen et al. 2014a, b). Osteoclasts are known to cause bone erosion, indicating the importance of these cells in bone destruction in alphavirus-induced pathology (Noret et al. 2012; Phuklia et al. 2013; Chen et al. 2014a, b).

Innate Immune Response and Inflammation

Fever experienced by all CHIKF patients could be attributed to cytokines such as IL-1 β , IL-6, and TNF- α , which are known pyretics (Ng et al. 2009). These cytokines have also been detected at high levels in acutely infected patients (Chow et al. 2011; Wauquier et al. 2011; Kelvin et al. 2011) and the levels returned to normal after fever and viremia have disappeared (Chow et al. 2011; Wauquier et al. 2010; Kelvin et al. 2011).

Arthralgia experienced by CHIKF patients closely resembles the symptoms induced by other alphaviruses (Pialoux et al. 2007; Powers and Logue 2007; Suhrbier and La Linn 2004). It is characterized by severe joint pain due to inflammation and tissue destruction caused by inflammatory cytokines such as IL-1 β , IL-6, and TNF- α as reported in CHIKF patients (Ng et al. 2009; Hoarau et al. 2010; Chow et al. 2011). Prostaglandins have also been shown to be highly expressed by CHIKV-infected fibroblasts (Fitzpatrick and Stringfellow 1980) and may contribute to mechanisms of nociceptor activation and sensitization as described in osteoarthritis joints (Fitzpatrick and Stringfellow 1980; Malfait and Schnitzer 2013).

The specific involvement of cytokines and chemokines have shown IL-1 β , IL-6, and RANTES to be associated with disease severity during the acute phase, thus enabling the identification of patients with poor prognosis and monitoring of the disease (Ng et al. 2009). Higher concentrations of pro-inflammatory factors such as IFN- α , IL6, and IP-10 were also found in patients with alphavirus-induced polyarthrititis than in patients without, indicating a potential causative role in chronic joint and muscle pains (Hoarau et al. 2010; Ng et al. 2009; Wauquier et al. 2011). Different patient cohorts have reported different patterns of the inflammatory immune mediators, suggesting that the basal levels of these mediators differ in the different populations (Teng et al. 2015). Specifically, pro-inflammatory cytokines such as IL-6, MCP-1, and IFN- α were found to be elevated during the acute phase of the disease in several patient cohorts (Ng et al. 2009; Hoarau et al. 2010; Chow

et al. 2011; Kelvin et al. 2011; Wauquier et al. 2011). Positive correlation was also observed between the expression of IL-6 or MCP-1 and the high viral load in CHIKV-infected patients (Chow et al. 2011). Interestingly, IL-6 and GM-CSF were also observed to associate with persistent arthralgia (Hoarau et al. 2010; Chow et al. 2011). A meta-analysis comparative study demonstrated that pro-inflammatory cytokines such as IFN- α , IFN- β , IL-2, IL-2R, IL-6, IL-7, IL-12, IL-15, IL-17, and IL-18; anti-inflammatory cytokines such as IL-1Ra, IL-4, and IL-10; chemokines: granulocyte colony-stimulating factor (GM-CSF), IP-10, MCP-1, monokine induced by gamma interferon (MIG), macrophage inflammatory protein (MIP) 1 α and MIP-1 β ; and growth factor: basic fibroblast growth factor (FGF) formed a generic acute CHIKV signature in all the different patient cohorts around the world (Teng et al. 2015). Although their respective roles are not fully understood, the various biomarkers indicated the important role that cytokines play in the pathology of CHIKV infection and can potentially lead to the development of modulators to reduce disease severity and halt disease progression.

The production of type I interferons, IFN- α and IFN- β , is the signature of an antiviral state in vertebrate hosts and they are essential to the functioning of the innate immunity against the replication and spread of virus. Type I IFNs and IFN-stimulated genes (ISGs) act through diverse mechanisms against viral invasions (Akira and Takeda 2004; Stetson and Medzhitov 2006). Although CHIKV was first reported to be a potent inducer of type I IFNs during infection as early as the 1960s (Gifford and Heller 1963), their roles in CHIKV infections are poorly known. Studies in patient cohorts have shed light on the interplay between type I IFNs and CHIKV during infections (Ng et al. 2009; Chow et al. 2011; Hoarau et al. 2010; Schilte et al. 2010), and experimental animal models have deciphered the role of RIG-I like receptors, Toll-like receptors, IRF 3/7, and interferon-stimulated genes (ISG15, Viperin, OAS) in limiting CHIKV replication (Brehin et al. 2009; Rudd et al. 2012; Schilte et al. 2012; Teng et al. 2012).

The role of type I IFN in CHIKV pathogenesis has been further investigated in human cells and mouse models. Data showed that infected nonhematopoietic cells sense viral RNA in a Cardif-dependent manner and participate in the control of infection through their production of type I IFN. Although the MAVS (also known as Cardif or IPS1) pathway contributes to the immune response both in cell culture of human fibroblasts and in mice, evidence for a MyD88-dependent sensor in preventing viral dissemination was demonstrated only in mice. It has been shown that interferon type I receptor (IFNAR) expression is required in nonhematopoietic cells but not in hematopoietic cells, as IFNAR^{-/-} \rightarrow WT bone marrow chimeras are able to clear the infection, whereas WT \rightarrow IFNAR^{-/-} chimeras succumb to disease. These data define an essential role for type I IFN, acting directly on nonhematopoietic cells, most likely fibroblasts, for the control of CHIKV (Schilte et al. 2010), although treatment with type I IFN is not a viable therapy when given after virus infection (Gardner et al. 2010). Other studies have also demonstrated that IRF3/IRF7-deficient mice developed hemorrhagic fever and shock after CHIKV infection (Rudd et al. 2012). Therefore, young age and inefficient type-I IFN signaling are risk factors for severe CHIKV disease.

Adaptive Immune Response and Protection

CHIKF leads to a protective adaptive immunity. The establishment of anti-CHIKV immune response after a primary infection could confer complete protection against reinfection. This provided the basis of the time-lapse between CHIKF epidemics (Laras et al. 2005). Anti-CHIKV IgM and IgG antibodies have been detected in the sera of infected patients during the acute phase of the infection (Panning et al. 2008; Kam et al. 2012a, b). The ability of anti-CHIKV antibodies to neutralize virus infectivity was also demonstrated by using sera from convalescent patients (Couderc et al. 2009; Kam et al. 2012a, b, c). These findings suggest that anti-CHIKV antibodies could be used as a potential prophylactic strategy against CHIKF (Couderc et al. 2009; Bréhin et al. 2008; Lee et al. 2011; Kam et al. 2012b, c; Pal et al. 2013; Smith et al. 2015). Therefore, viremic mothers and neonates born of viremic mothers, patients with severe neurological presentation of the disease, small infants, or adults with severe underlying comorbidities could benefit from passive immunization using anti-CHIKV immunoglobulins.

The importance of B cells was also demonstrated in B cell (μ MT) knock-out mice infected with CHIKV, where viremia in these animals persisted for over a year, indicating a direct role for B cells in mediating CHIKV clearance (Lum et al. 2013). These animals exhibited a more severe disease than wild-type mice during the acute phase.

Antibody-mediated protection against CHIKV has been studied extensively for vaccine development (Ahola et al. 2015) and surface viral glycoproteins have been demonstrated to be key targets for protective neutralizing antibodies against CHIKV alphaviruses (Bréhin et al. 2008; Lee et al. 2011; Kam et al. 2012b, c; Pal et al. 2013). It was shown that immunization with CHIKV virus-like particle (VLP) vaccines and other vaccine candidates comprising key surface viral glycoproteins could induce the production of neutralizing antibodies and protect both mice and nonhuman primates against CHIKV challenge (Akahata et al. 2010; Kam et al. 2012b; Metz et al. 2013a, b; Hallengard et al. 2014; García-Arriaza et al. 2014; van den Doel et al. 2014; Roy et al. 2014). More recently, the first CHIKV VLP vaccine (Akahata et al. 2010) was successfully demonstrated to be well tolerated and protective in human trials, making it a significant breakthrough (Chang et al. 2014).

T cells are important effector cells during viral infection. Both $CD4^+$ and $CD8^+$ T cells can eliminate virus-infected cells. Adult $RAG2^{-/-}$, $CD4^{-/-}$, $CD8^{-/-}$, and wild-type C57BL/6 CHIKV-infected mice have demonstrated the importance of T cells in CHIKV-induced pathology (Teo et al. 2013). Interestingly, results indicated that CHIKV-specific $CD4^+$ but not $CD8^+$ T cells are essential for the development of joint swelling without any effect on virus replication and dissemination (Teo et al. 2013; Hawman et al. 2013). These observations strongly indicate that mechanisms of joint pathology induced by CHIKV in mice resemble those in humans, and differ from infections caused by other arthritogenic viruses such as Ross River virus (Morrison et al. 2006). Furthermore, using mice deficient for MHC II and $IFN-\gamma$, gene set enrichment analysis showed a significant overlap in differentially expressed genes from CHIKV arthritis and rheumatoid arthritis (Nakaya et al. 2012).

Challenges and Limitations to Fully Understand CHIKV Chronicity

To conclude, CHIKV infections induce a self-perpetuating pro-inflammatory reaction that causes arthralgia, explaining why pains are constant ailments in many patients with persistent joint-associated CHIKV even years after recovery from the initial febrile phase (Hoarau et al. 2010). No animal model could fully reproduce the chronic rheumatoid syndrome following CHIKV. Indeed, the disease pathology reported in mice is mainly driven by destruction of tissues with huge cell infiltration that could only be resolved 1–2 weeks after acute disease (Gardner et al. 2010; Morrison et al. 2011; Rulli et al. 2011). Despite virus persistence, severe joint damage is not always observed in macaques which could reflect the estimated scenario where only 5 % of patients meet the criteria for chronic inflammatory rheumatism (rheumatoid arthritis, spondyloarthritis, or unclassified polyarthritis; Chen et al. 2010; Labadie et al. 2010; Simon and Gasque 2015). Nevertheless, both animal models present inflammation, macrophage tissue tropism, and virus persistence in tissues (Labadie et al. 2010; Hawman et al. 2013). However, the exact mechanism in the establishment of chronic disease induced by CHIKV infection remains undefined.

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