



# Pathogenesis of chronic chikungunya arthritis: Resemblances and links with rheumatoid arthritis

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## ABSTRACT

Chikungunya virus (CHIKV) infection results from transmission by the mosquito vector. Following an incubation period of 5–7 days, patients develop an acute febrile illness, chikungunya fever (CHIKF), characterized by high fevers, maculopapular rash, headaches, polyarthritis/arthralgias, myalgias, nausea, vomiting, and diarrhea. Joint pain is often severe, and most often involves the hands, the wrists, the ankles, and the metatarsal-phalangeal joints of the feet. Many patients recover within several weeks, but up to 50% develop chronic joint pain and swelling for more than 12 weeks, then we refer to these symptoms as chronic chikungunya arthritis (CCA). The pathogenesis of CCA is not well understood. In this article, we suggest that mesenchymal stem cells (MSCs) may play an important role in this pathogenesis. This heterogeneous group of multipotent cells, morphologically similar to fibroblasts, may undergo epigenetic changes capable of generating aberrant progenies. However, we believe that there is no need for a latent infection. In our pathogenic hypothesis, CHIKV infection of MSCs would cause epigenetic changes both in MSCs themselves and in their progenies, without the need for reactivation of dormant viruses.

## 1. Introduction

Chikungunya is caused by the chikungunya virus (CHIKV), a small (60–70 nm, 12 Kb), single-stranded positive-sense RNA arbovirus in the *Alphavirus* genus of the *Togaviridae* family, transmitted by *Aedes* species mosquitoes [1]. Only 5% of infected individuals are asymptomatic [2]. CHIKV infection causes a biphasic illness. The acute phase “chikungunya fever” (CHIKF) is characterized by the abrupt onset of high fever, disabling polyarthritis, and maculopapular rash associated with other symptoms including headache, myalgia, nausea, and vomiting [3]. Following the acute phase, 40–59% of patients develop chronic symptoms, primarily chronic chikungunya arthritis (CCA) [4]. These patients can have painful, destructive inflammatory arthritis that often mimics rheumatoid arthritis (RA) and related disorders [5,6]. During recent widespread epidemics, CCA has caused substantial morbidity, disability, and in some cases, irreversible joint destruction [7,8].

CHIKV was first isolated in 1952 in Tanzania, during an outbreak on the Makonde plateau. The word “chikungunya” means “that which bends up” or “to become contorted” in the Makonde language, referring to the prostrated appearance of affected patients [9,10]. Since the first reports of CHIKV infection in Africa in the 1950s, subsequent epidemics of CHIKV occurred during the second half of the 20th century in countries in Asia and sub-Saharan Africa [3]. More recently, CHIKV has caused intermittent outbreaks in Africa, Asia, the Indian Ocean islands, and in southern Europe [11].

CHIKF is generally self-limiting and has a low mortality rate (~0.1%) [10], but neurological complications, including encephalitis, optic neuritis, facial paralysis, sensorineural deafness, and Guillain-Barré syndrome, occur in up to 25% of patients [12,13]. Rarely, CHIKV infection causes myocarditis, cardiac arrhythmia, severe sepsis, and septic shock [13]. In addition, CHIKV infection manifestations that lead to acute and chronic disability can have considerable social and

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economic implications, including a substantial impact on the quality of life of infected patients [7,14].

A number of reports have characterized CCA as “post-chikungunya chronic inflammatory rheumatism” and described CHIKV-infected patients who develop arthritis resembling rheumatoid arthritis (RA), seronegative spondyloarthritis (SpA), psoriatic arthritis (PsA) and undifferentiated polyarthritis (UP), defined as the presence of inflammatory arthritis affecting more than 4 joints of greater than 6 weeks duration in the absence of an alternative diagnosis (Table 1) [4,15–17].

No specific antiviral treatment has been shown to be effective against CHIKV. [18,19]; therefore, treatment during the acute phase consists of supportive therapy. The goals of CCA treatment include pain relief and preventing joint destruction. A spectrum of treatment options, including nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, hydroxychloroquine (HCQ), sulfasalazine (SSZ), leflunomide, methotrexate (MTX), and biologic agents, alone or in combination, have been considered [15].

There are intriguing similarities in immunological phenotypes of peripheral blood mononuclear cells of patients with RA and CCA, but the pathobiology of CCA is not well understood [20]. Both diseases may involve similar mechanisms. For example, in some studies, CCA has been associated with high circulating levels of pro-inflammatory cytokines including IL-6, GM-CSF, IFN- $\alpha$ , and IL-17 [21]. Hypotheses regarding the pathogenesis of CCA include the persistence of a low level of replicating virus in the joints, the persistence of viral RNA in synovium, and the induction of autoimmunity [20–23]. Muscle satellite cells and synovial macrophages have been proposed as reservoirs for persistent CHIKV in humans, suggesting that persistent CHIKV antigen, or perhaps chronic infection, triggers an inflammation that culminates in CCA [23].

Much has been said about the cytokines, chemokine patterns and cell types involved in the pathogenesis of CCA. However, these are common ingredients involved to a greater or lesser extent in various rheumatic diseases that result in inflammation and pain. In this article, we propose a hypothesis as to how CHIKV infection initiates a series of events that result in a condition that resembles RA. We hypothesize that mesenchymal stem cells (MSCs) infected by CHIKV [24] may be implicated in the development of a chronic aberrant immune response in CCA and other rheumatic diseases such as RA. Similarities between pathogenic mechanisms in CCA and RA [25] may lead to a common link: mesenchymal stem cells (MSCs). CHIKV may be another example of a viral infection [25–27] that triggers an immune cascade through changes in progenitor cells causing RA, CCA and other inflammatory chronic diseases.

In RA, stable epigenetic marks have been identified that permanently alter cell function and imprint some cells, especially fibroblast-like synoviocytes (FLS), through widespread DNA hypomethylation, histone modification and miRNA expression [28–30]. This leads to the question: is there a common cell capable of generating defective progenies from an infectious stimulus? This might explain the association of several viruses in the pathogenesis of RA and the development of an RA-like illness in CCA.

We suggest that mesenchymal stem cells (MSCs) may play this role. This heterogeneous group of multipotent cells, morphologically similar to fibroblasts, which form colonies and are capable of differentiating into mesenchymal lineage cell types, including osteogenic and chondrogenic, may undergo epigenetic changes capable of generating aberrant progenies [30]. Some studies have shown that the increase in local production of TNF $\alpha$  can damage the bone marrow (BM) microenvironment and affect the reserves of BM hematopoietic progenitor cells [31]. It has been postulated that infections can affect BM MSCs and transmit pathogens to their progeny. According to this hypothesis, transient but repeated reactivation of dormant viruses or bacteria can promote the conversion of BM regulatory T cells into effector phenotypes, leading to autoimmunity in the epiphyseal BM, entheses and adjacent synovium [32]. However, we believe that there is no need for a latent infection. In our pathogenic hypothesis, CHIKV infection of MSCs would cause

epigenetic changes both in MSCs themselves and in their progenies, without the need for reactivation of dormant viruses. This would help us to explain why CHIKV is not found in patients with CCA. In this review, we have gathered evidence that this is possible.

## 2. Chikungunya virus infection

CHIKV is a positive stranded, enveloped RNA virus. The genome has five structural proteins; E1, E2, E3, C (Capsid protein), 6 K and four non-structural proteins; non-structural proteins 1 (nsP1), 2 (nsP2), 3 (nsP3) and 4 (nsP4) [33]. CHIKV is transmitted horizontally to vectors during a blood meal in a viremic host and reaches the midgut, and replicates. Seven days after infection, the virus reaches the vector's salivary glands [34].

The first step in infection involves binding the virus to a host cell receptor, such as dermal fibroblasts, migrating monocytes/macrophages and endothelial cells. These receptors include prohibitin, receptors that improve the entry of viruses mediated by phosphatidylserine (PtdSer), glycosaminoglycans,  $\alpha$ V integrin and  $\beta$ 1 integrin dimer, and Heat shock protein 60 (Hsp60) [34,35].

After E2-mediated binding to cells, the particles bound to the receptor are internalized mainly by clathrin-mediated endocytosis, similar to other alphaviruses [10,35]. Conformational changes in viral E1 and E2 glycoproteins are induced by endosomal acidification, generating exposure and insertion of the E1 fusion loop buried in the host membrane. This promotes the fusion of the viral envelope and the endosomal membrane [36,37]. After release into the cytoplasm, the nucleocapsid disassembles to provide genomic viral RNA (vRNA) in the cytosol for translation [33]. However, CHIKV can also enter cells via an epidermal growth factor receptor-dependent pathway, independent of clathrin, (Eps15), or enter human muscle cells through macropinocytosis [37,38]. The replication of this alphavirus strongly affects the fundamental processes of cell physiology, with inhibition of transcription and translation and redirection of cellular resources to the synthesis of proteins and viral genomes [39].

CHIKV infects susceptible cells in the dermis, such as endothelial cells, fibroblasts and macrophages, and replicates rapidly through the mechanism summarized above. Viral particles produced locally are transported by the circulatory system to secondary lymphoid organs and then disseminated to different organs, including the brain, spleen, liver, joints and muscles [40]. However, bone marrow-derived mesenchymal stem cells (BMSC) and BMSC-derived osteogenic cells have also recently been shown to be susceptible to CHIKV infection [41].

The innate immune response against viruses consists of macrophages, dendritic cells (DCs) and natural killer cells (NKs) and is followed by the activation of the adaptive immune response mediated by B and T lymphocytes [42]. After cell infection, the CHIKV RNA genome can trigger host pattern recognition receptors (PRRs), inducing interferon type I-dependent (IFN) antiviral responses. This PRR and IFN signaling induces the secretion of pro-inflammatory cytokines and chemokines, which recruit innate and adaptive immune cells to sites of the infection that causes inflammation [39,43]. Studies in mice, some species of non-human primates and in humans have shown that levels of various pro-inflammatory cytokines and chemokines, including IL-1R $\alpha$ , IL-2R, IL-5, IL -6, IL-7, IL-10, IL-15, IFN- $\alpha$ , CXCL9, CXCL10, HGF, FGF-basic and VEGF, are increased during acute CHIKV infection, [43, 44]. In fact, several studies have identified elevated plasma levels in CHIK patients with multiple soluble factors, including cytokines CCL2, CCL4, CXCL10, IL - 6, IL - 8 and IL - 16), anti-inflammatory cytokines (IL1-ra, IL and IL - 13), growth factors (granulocyte colony stimulating factor [G-CSF], granulocyte-macrophage colony stimulating factor [GM-CSF], vascular endothelial growth factor and stem cell growth factor  $\beta$ ) and other mediators (IFN $\gamma$ , IL - 4, IL - 7), in addition to those already mentioned [45]. As a result, there is an accumulation of monocytes in infected tissues and activation of CD8 + T cells and natural killer (NK) to help eliminate the virus [46].

**Table 1**  
Chronic chikungunya arthritis articles selected.

Objective	Type of Study	Number of Subjects	Results	Methods	Author, year and country [Reference]
To determine the percentage of patients who would develop (CIR)	Systematic Review and Meta-Analysis	5702	The pooled prevalence of CHIK-CIR was 40.22%	Systematic review of the literature in 3 databases (PubMed, Science Citation Index, and Scopus)	Rodríguez-Morales et al., 2016, Colombia [4]
To describe the clinical spectrum of CCA and to report The experience treating CCA with (MTX)	Retrospective study	50	At W0: mean VAS was 7.7 (SD, 2.0). The mean reductions from baseline pain at W4 and W8 were, respectively, 4.3 (3.0) ( $p < 0.0001$ ) and 4.5 (2.6) ( $p < 0.0001$ ), respectively.	CCA patients were evaluated at a baseline visit and at follow-up at 4 and 8 weeks. Demographic features were obtained along with a medical and rheumatologic history that included any previous rheumatic disease. Patient symptomatic activity was assessed at each visit VAS	Amaral et al., 2018, Brazil [5].
To report cases of RA after CHIKV infection	Prospective study	21	Twenty-one patients fulfilled RA criteria. Eighteen patients (85.7%) had symmetric polyarthritis and three had oligoarthritis. The mean ESR was $40.7 \pm 28.1$ mm/h and C-reactive protein level $37 \pm 41$ mg/l; 12 patients were positive for rheumatoid factor (57.1%), and six had anti-CCP antibodies (28.6%)	Patients were examined by the same rheumatologist from February 2006 to July 2007. Inclusion criteria were (1) Chikungunya infection confirmed by IgM and IgG antibodies, (2) RA according to ACR criteria, (3) no other definite diagnosis of arthritis and (4) persistent arthritis symptoms from the onset of viral infection to RA diagnosis.	Bouquillard and Combe, 2009, France [6]
To see to what extent the subjective health differences observed in 2008 (30 months after infection) between CHIK infected (CHIK+) and noninfected (CHIK-) gendarmes still persisted in 2012, and to investigate a possible return to a pre-CHIK health status for CHIK + subjects.	Prospective observational study	252	CHIK + patients complained of more frequent and intense joint pain than CHIK - (38% vs. 17% declared suffering at least once a week; 48% vs. 16% declared moderate to intense pain, $p = 0.0001$ . Stiffness once per month was declared at least 3 times more frequently by CHIK + than by CHIK- subjects, and swelling 10 times more frequently	Using data from the Gendarmerie headquarters, 646 participants in the 2006 enquiry were identified and sent letters containing information on the previous follow-up results, a description of the current study's purpose, an informed consent form to participate, a separate proposal for new biological tests (data not presented due to low acceptance rate) and a self-questionnaire.	Marimoutou et al., 2015, France [7]
To better define the spectrum of pain and disability in CCA	Retrospective study	35	The mean time elapsed between the onset of CHIKF and evaluation in our clinic was $21.6 \pm 2.85$ months. During the initial visit, 27 patients (77%) reported severe pain (VAS 7–10), seven (20%) had moderate pain (VAS 4–6), and only one (3%) reported mild pain (VAS 1–3). Mean pain level for the entire group was $8.02 \pm 1.82$ .	Were evaluated consecutive CCA patients seen in a rheumatology clinic, using a pain VAS and the Health Assessment Questionnaire Disability Index.	Amaral et al., 2019, Brazil [8]
To describe the frequency of prolonged clinical manifestations of CHIKV infection and to measure the impact on quality of life and health care consumption in comparison with that of an unexposed population	Retrospective cohort study	398	CHIK + complained more frequently than CHIK- of arthralgia (relative risk = 1.9; 95% confidence interval: 1.6–2.2), myalgia (1.9; 1.5–2.3), fatigue (2.3; 1.8–3), depression (2.5; 1.5–4.1) and hair loss (3.8; 1.9–7.6). The mean (SD) score of the SF-12 Physical Component Summary was 46.4 (10.8) in CHIK + versus 49.1 (9.3) in CHIK- ( $p = 0.04$ ). There was no significant difference between the two groups for the Mental Component Summary.	199 subjects who had serologically confirmed CHIKV infection (CHIK+) were compared with 199 seronegative subjects (CHIK-) matched for age, gender and area of residence in La Réunion Island. Following an average time of 17 months from the acute phase of infection, participants were interviewed by telephone about current symptoms, medical consumption during the last 12 months and quality of life assessed by the 12-items Short-Form Health Survey (SF-12) scale.	Soumahoro et al., 2009, France [14]
To describe the common mechanical and inflammatory post-CHIK disorders. To provide a diagnostic and therapeutic algorithm to help physicians deal with chronic patients, and to limit both functional and economic impacts.	Retrospective study	159	Ninety-four patients (59%) who were free of any articular disorder prior to CHIK met the CIR criteria: RA ( $n = 40$ ), spondyloarthritis ( $n = 33$ ), undifferentiated polyarthritis ( $n = 21$ ). Bone lesions detectable by radiography occurred in half of the patients (median time: 3.5 years pCHIK). A positive therapeutic response was achieved in 54 out of the 72 patients (75%) who were treated with MTX. Twelve out of the 92 patients (13%) received immunomodulatory biologic agents due to failure of contra-indication of MTX treatment.	A 6-year case series retrospective study in Reunion Island of patients referred to a rheumatologist due to continuous rheumatic or musculoskeletal pains that persisted following CHIK infection. These various disorders were documented in terms of their clinical and therapeutic courses. Post-CHIK de novo chronic inflammatory rheumatisms (CIRs) were identified according to validated criteria.	Javelle E. et al., 2015, French Reunion Island [15]

Table 1 (continued)

Objective	Type of Study	Number of Subjects	Results	Methods	Author, year and country [Reference]
To investigate in details the long-term outcome of CHIK	Prospective cohort longitudinal study		During the 3 years following acute infection, 60% of patients had experienced symptoms of arthralgia, with most reporting episodic relapse and recovery periods. Long-term arthralgias were typically polyarthralgia (70%), that were usually symmetrical (90%) and highly incapacitating (77%). They were often associated with local swelling (63%), asthenia (77%) or depression (56%)	Patients were submitted to clinical investigations 4, 6, 14 and 36 months after presentation with acute CHIKV infection. At 36 months, 22 patients with arthralgia and 20 patients without arthralgia were randomly selected from the cohort and consented for blood sampling.	Schilte et al., 2013, French Reunion Islande [16]
To assess a cohort of post-CHIK-CIR in Latin America, at the municipality of La Virginia, Risaralda, a new endemic area of CHIK in Colombia.	Cohort retrospective study	283	152 (53.7%) reported persistent rheumatological symptoms (pCHIK-CIR). All of these patients reported joint pains (chronic polyarthralgia, pCHIK-CPA), 49.5% morning stiffness, 40.6% joint edema, and 16.6% joint redness. Of all patients, 19.4% required and attended for care prior to the current study assessment (1.4% consulting rheumatologists).	Was conducted a cohort retrospective study in Colombia of 283 patients diagnosed with CHIK that persisted with pCHIK-CIR after a minimum of 6 weeks and up to a maximum of 26.1 weeks. pCHIK cases were identified according to validated criteria via telephone.	Rodriguez-Morales et al., 2016, Colombia [17]
To assess the prevalence of and risk factors for chronic musculoskeletal symptoms and for a RA-like condition at 27.5 months after initial infection.	Prospective study	173	136 (78.6%) reported persisting musculoskeletal symptoms 27.5 months after infection. Persistent symptoms were associated with older age at time of infection, female gender and baseline symmetrical distribution of joint symptoms. 5% of those infected with CHIKV fulfilled a modified version of the ACR criteria for RA 27.5 months after infection.	Participants were recruited May–November 2008 and invited to complete a questionnaire. CHIKV was diagnosed clinically. The primary outcomes for the analyses were (a) self-reported ongoing musculoskeletal symptoms and (b) fulfilment of modified diagnostic criteria for rheumatoid arthritis. Risk factors for these outcomes were explored in univariate analyses using logistic regression. Subsequently, multivariate logistic regression was used to identify factors that were independently associated with the outcomes.	Essackjee et al., 2013, Mauritius [47]
To describe the clinical features of CHIKF during the first and tenth months of illness.	Prospective longitudinal study	203	During the acute stage CHIKF presents with a wide array of symptoms. The foremost chronic symptoms at the end of a month were rheumatism (75%) and fatigue (30%). During the tenth month of follow-up the symptoms/signs observed were joint pain/swelling (46%), fatigue (13%) and neuritis (6%). The cure rate at the end of 9 months was 51%. Among the patients who had joint pain, 36% (34/94) met the ACR criteria to classify them as having RA.	Patients were recruited from the primary health centre and all four sub-centres under its jurisdiction. A structured questionnaire was used for eliciting necessary information. A clinician interviewed the patients on the first day of illness at the health facility and on subsequent days of follow-up (days 2, 3, 7, 14, 21, 30) at their houses. During the tenth month of illness all the laboratory-confirmed patients with CHIKV infection were examined by the same clinician. The symptoms and signs were recorded	Manimunda et al., 2010, India [48]
To detail the prevalence of pCHIK chronic polyarthralgia (pCHIK-CPA) in patients that suffered from confirmed CHIK at least 6 weeks before current assessment with a maximum follow-up of 65 weeks (15 months) (median time of 35 weeks).	Retrospective study	39	From 39 patients that suffered CHIK 89.7% developed persistent polyarthralgia (pCHIKCPA) that met the ACR/EULAR 2010 criteria for (seronegative) RA.	39 patients that suffered CHIK (diagnosed by PCR during acute phase) were evaluated between April 2014 and May 2015 who attended in Since, Sucre (one of the newly endemic departments), Colombia,	Rodríguez-Morales et al., 2015, Colombia [49]

CHIK: chikungunya; CHIKF: chikungunya fever; CHIKV: chikungunya virus; CCA: chronic chikungunya arthritis; pCHIK-CIR: postchikungunya chronic inflammatory rheumatism; CIR: chronic inflammatory rheumatism; VAS: pain Visual Analog Scale; RA: rheumatoid arthritis; ESR: erythrocyte sedimentation rate; MTX: methotrexate; ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology.

### 3. Chronic chikungunya arthritis and rheumatoid arthritis

In many patients, CCA clinically mimics RA (Table 2). Some studies report patients with CCA whose clinical features are so similar to rheumatoid arthritis that they meet the 2010 American College of Rheumatology (ACR) diagnostic criteria for RA [5,6,20]. Among 173 patients with CHIKV evaluated at 27.5 months, Essackjee et al. reported that 78.6% had persistent musculoskeletal symptoms and 5% met 2010 American College of Rheumatology/European League Against

Rheumatism (ACR/EULAR) criteria for RA [47]. In an Indian study, among 203 patients with CHIKF who developed joint pain, 36% (34/94) met the ACR/EULAR criteria for RA [48]. In other reports, RA mimics have been even more frequent. In a Colombian study, 35 of the 39 patients, and in an American study, 8 of 10 patients, with CHIKF developed arthritis that met RA ACR/EULAR criteria (Table 1) [49,50].

As in RA, most patients with CCA are middle-aged and are women [4, 5,51]. Commonly affected joints include the metacarpophalangeal, proximal interphalangeal, and wrist joints as well as the knees and



**Table 2**  
Similarities and differences between chronic chikungunya arthritis (CCA) and rheumatoid arthritis (RA).

	Chronic chikungunya arthritis (CCA)	Rheumatoid arthritis (RA)
<b>Similarities</b>	<p><b>Presentation:</b> small joint symmetric polyarthritis (most commonly). <b>Patients:</b> middle-aged females (most commonly affected demographic). <b>Symptoms:</b> fatigue, arthralgias, arthritis, myalgias, and morning stiffness. <b>Labs:</b> normochromic anemia; thrombocytosis, and elevated ESR/CRP, RF may be reactive. <b>Radiographic:</b> joint effusions, bone erosions, marrow edema, synovitis, tendinitis, and/or tenosynovitis. <b>Serum cytokine profile:</b> ↑ IL-1β, IL-6, IL-17, and TNF (chronic disease) <b>Synovial cytokine profile:</b> ↑ IL-1β, IL-6, IL-7, IL-8, IL-10, IL-15, IL-17, GM-CSF, IFN-α, IFN-γ, and TNF (chronic disease) <b>Pathogenesis:</b> FLS important in perpetuating inflammation and joint <b>Disability:</b> can be moderate-to-severe (chronic disease) <b>Therapy:</b> improvement with the use of methotrexate and corticosteroids and possibly other DMARDs</p>	
	Chronic chikungunya arthritis (CCA)	Rheumatoid arthritis (RA)
<b>Differences</b>	<p><b>Presentation:</b> medium and/or large joint asymmetric mono- or oligoarthritis (less commonly). <b>Signs and Symptoms:</b> neuropathic pain, memory and concentration problems and asthenia/depression can be more predominant than in RA. <b>Serologies:</b> anti-CHIKV IgM and/or IgG antibodies.</p> <p><b>Causative pathogen:</b> chikungunya virus (CHIKV)</p> <p><b>Serum cytokine profile:</b> ↑ IL-1RA, IL-1β, IL-6, IL-7, IL-8, IL-12, IL-15, and IFN-α (during acute arthritis); ↓ CCL5/RANTES (during acute arthritis); ↑ GM-CSF and TNF (during chronic arthritis).</p>	<p><b>Presentation:</b> usually insidious and known etiology</p> <p><b>Signs and Symptoms:</b> association with pulmonary (interstitial) disease and/or rheumatoid nodules, systemic involvement</p> <p><b>Serologies:</b> anti-cyclic citrullinated peptide antibodies (anti-CCP); rheumatoid factor (RF)</p> <p><b>Causative pathogen(s):</b> EBV, CMV, HIV, HTLV-I, HCV, and others (implicated in the pathogenesis)</p> <p><b>Serum cytokine profile:</b> ↑ CCL5/RANTES correlates with disease severity.</p>

ESR (erythrocyte sedimentation rate); CRP (C reactive protein); TNF (tumor necrosis factor); GM-CSF (granulocyte macrophage-colony stimulating factor); CHIKV (chikungunya virus); EBV (Epstein-Barr Virus); CMV (Cytomegalovirus); HIV (Human Immunodeficiency Virus); HTLV-I (Human T-cell Lymphotropic Virus); HCV (Hepatitis C Virus); RF(rheumatoid factor); DMARDs (Disease Modifying Antirheumatic Drugs); FLS (fibroblast-like synoviocytes).

ankles in a symmetric, polyarticular pattern [48]. Joint swelling, bursitis, and tendonitis may occur [21]. Fatigue, insomnia, myalgias, morning stiffness, memory or concentration problems, and asthenia and depression are seen as in RA patients with co-existing fibromyalgia [9, 21,22]. In one study, most patients (90%) reported symmetrical joint involvement, 63% had joint swelling, and 39% had chronic myalgias [16]. Inflammatory markers such as ESR and CRP are usually elevated in patients with chronic musculoskeletal symptoms, and some patients develop radiographic evidence of joint damage [8]. In addition to these clinical similarities, a minority of CCA patients have positive rheumatoid factor [6] and, less commonly, positive anti-cyclic citrullinated peptide antibody test results [7,8].

**4. Bone marrow-derived mesenchymal stem cells and their possible role in CCA pathogenesis**

Mesenchymal stem cells (MSCs) are adult stem cells capable of differentiating into mesodermal, endodermal, and ectodermal lineage cells such as endothelial cells, adipose cells, bone and cartilage,

hepatocytes, among others. MSCs can be isolated from BM, adipose tissue, umbilical cord, and skeletal muscle [52]. MSCs derived from BM are called bone marrow-derived mesenchymal stem cells (BMMSCs) and have a greater degree of commitment to differentiate into chondrogenic and osteogenic lineages than MSCs from other tissues [53].

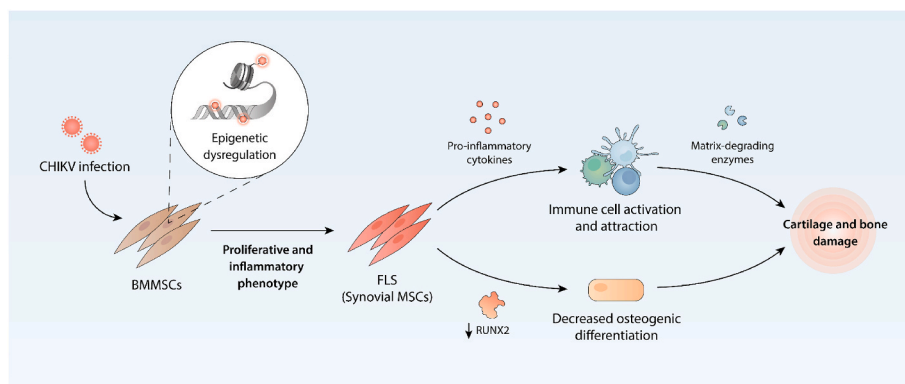
One type of synovial MSCs (S-MSCs), FLS are particularly important in perpetuating inflammation and joint destruction in RA and osteoarthritis [54,55]. FLS mediates inflammation and autoimmune responses through the production of pro-inflammatory molecules such as interleukin IL-1β, IL-6, and TNF-α, as well as secretion of MMPs through activation of multiple intracellular signal transduction pathways, including extracellular signal-regulated protein kinase (ERK), c-Jun N terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) [56]. In fact, recent studies suggest that FLS are responsible for the cartilage damage characteristic of RA [57].

Despite their role in populating the intimal lining of the synovium and contributing to the structural and dynamic integrity of normal joints, in RA, FLS increase in number and become an important component of the destructive pannus typical of RA synovium [58]. In CCA, change in FLS functionality may similarly result from epigenetic mechanisms induced by CHIK infection [59–62].

In fact, many viruses can utilize host cellular pathways that result in altered cell identity, through the induction of epigenetic and expression changes that induce autoimmunity. One example is the Epstein-Barr virus (EBV) which is associated with autoimmune diseases such as RA, systemic lupus erythematosus (SLE) Sjögren’s syndrome and multiple sclerosis (MS) possibly through epigenetic mechanisms [63,64]. Other examples of infectious agents associated with autoimmunity are parvovirus, associated with arthritis, and human cytomegalovirus (HCMV), which has been linked to psoriatic arthritis, Sjögren’s syndrome, inflammatory myositis, psoriasis, granulomatous vasculitis, ulcerative colitis, and Crohn’s disease [65]. Some evidence suggests that BM-MSCs may behave aberrantly and/or are epigenetically modified in RA following exogenous triggers [32,66]. It has been postulated that transient but repeated activation of dormant viruses such as EBV or bacteria such as *Tropheryma Whipplei* could promote the conversion of marrow regulatory T cells into effector phenotypes, leading to autoimmunity in the BM of the epiphysis, entheses, and adjacent synovium [32].

One study demonstrated that CHIKV can infect BMMSCs and osteogenic cells *in vitro* and decrease gene expression of the main regulator of osteogenic differentiation, RUNX2, in osteogenic cells, in addition to decreasing alkaline phosphatase (ALP) production and activity and matrix mineralization, impairing impaired functional properties of these cells [41]. Furthermore, CHIKV infection altered the expression of several microRNAs (miRNAs), whose aberrant miRNAs are associated with the pathogenesis of several diseases, including viral infections [67–69]. MiRNAs are small unencoded RNAs that regulate major cellular functions through modulation of gene expression, including cell cycle, differentiation, proliferation, apoptosis and immune response and are considered the main epigenetic mechanisms for the control of expressed genes, including in mesenchymal stem cells [67,70,71].

CHIKV infection could alter epigenetic markers in BMMSCs and change some cellular phenotypes, such as FLS, causing them to permanently acquire an aggressive and proliferative phenotype. Such cells may initiate an inflammatory condition and produce many cytokines and chemokines that lead to the attraction and activation of other immune cells and eventually become key players in bone and cartilage destruction through regulation of matrix-degrading enzymes in the joint, as in RA (Fig. 1) [28,57]. It is important to note that the impact of epigenetic changes can be long-lasting, persisting through subsequent generations of cells during replication (also known as transgenerational gene regulation) [72,73].



**Fig. 1.** Bone marrow-derived mesenchymal stem cells and their possible role in chronic chikungunya arthritis pathogenesis.

Chikungunya virus (CHIKV) infection could alter epigenetic markers in bone marrow-derived mesenchymal stem cells (BMMSCs) and change some cellular phenotypes, such as fibroblast-like synoviocytes (FLS), causing them to permanently acquire an aggressive and proliferative phenotype. Such cells may initiate an inflammatory condition and produce many cytokines and chemokines that lead to the attraction and activation of other immune cells and eventually become key players in bone and cartilage destruction through regulation of matrix-degrading enzymes in the joint.

## 5. Conclusion

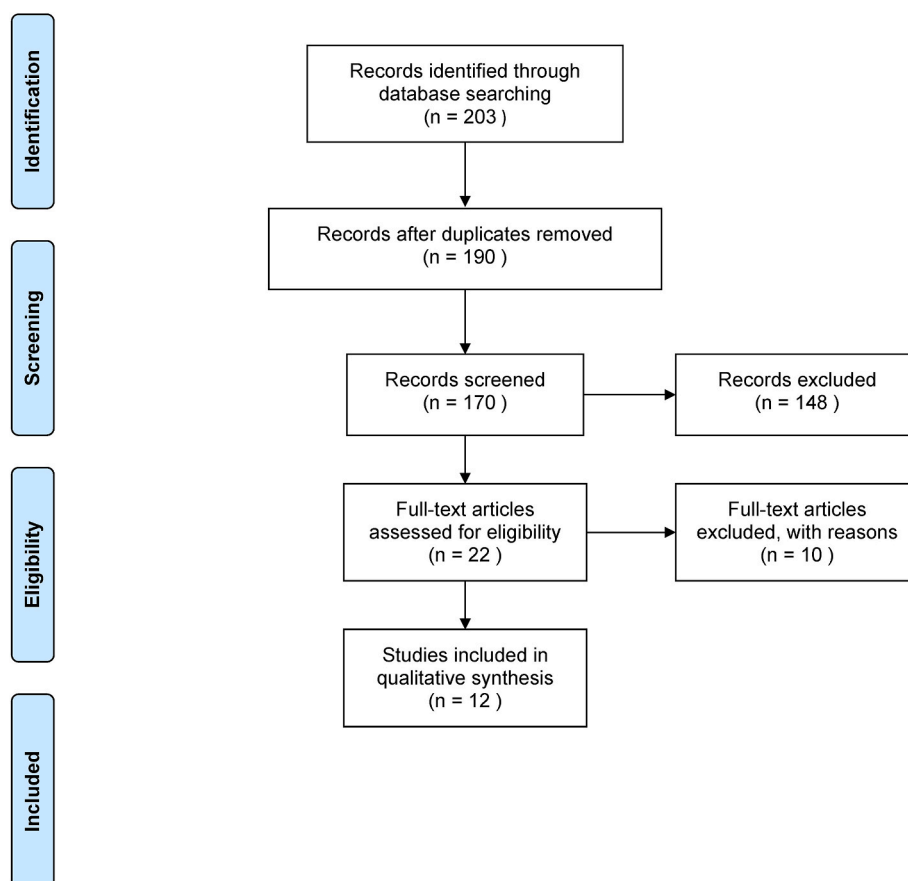
The clinical resemblance of CCA with RA is remarkable in several clinical aspects including the predominance in middle-aged women, joint involvement pattern and symmetry, elevation of inflammatory markers, radiographic changes, and positive response to corticosteroids and DMARDs. In fact, it is difficult to distinguish whether CCA patients actually have CCA or if CHIKV infection induced RA. The parallels between these entities are not unexpected based on their pathogenic mechanisms. Notably, there are several similarities in the cytokine profile, types of immune cells involved, and most recently, the possible role of FLS in both conditions.

We believe that there is no need for a latent CHIKV infection in the pathogenesis of CCA. In our hypothesis, CHIKV infection of MSCs causes epigenetic changes in both MSCs themselves and in their progenies,

without the need for reactivation of dormant viruses. This hypothesis would help to explain why CHIKV is not found in patients with CCA. Further studies on the role of epigenetic changes in CHIKV-infected BMMSCs are needed and may provide valuable information about the pathogenesis of CCA.

## 6. Search strategy and selection criteria

We searched PubMed using the search terms “Chikungunya”, “Chikungunya virus”, “Chikungunya infection”, “Chronic chikungunya arthritis”. We limited our search to articles that were published in English between 2005, and May 2022 (Fig. 2).



**Fig. 2.** Chronic chikungunya arthritis studies selected.

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## Author contributions

All authors have made substantial contributions to the conception of the work and have drafted the work or substantively revised it; A.N.D. has approved the submitted version; they agree to be personally accountable for their contributions and for questions related to the accuracy or integrity of any part of the work. Conceptualization: J. Kennedy Amaral., Peter Taylor, Clifton O. Bingham, Michael Weinblatt, Luis M. Vilá, Robert T. Schoen; Writing—Original Draft Preparation: J. Kennedy Amaral., Peter Taylor, Clifton O. Bingham, Michael Weinblatt, Luis M. Vilá, Robert T. Schoen; Writing—Review & Editing: J. Kennedy Amaral., Peter Taylor, Clifton O. Bingham, Michael Weinblatt, Luis M. Vilá, Robert T. Schoen.

## Declaration of competing interest

All authors declare no relevant competing interests.

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