COMMENTARY

# Closing the gap between viral and noninfectious arthritis

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Worldwide, mosquito-borne alphaviruses are a major cause of infectious arthritis-like disease, but this has not yet significantly impacted the Americas (1). The arthritogenic alphaviruses include Ross River virus (RRV), chikungunya virus (CHIKV), Sindbis-like viruses (SINV), Barmah Forest virus (BFV), Mayaro virus (MAYV), and o'nyong-nyong virus (ONNV), which are typically found from Europe to central Africa, southern Asia, and in portions of northern South America (2). Infection with these viruses begins as a febrile illness, which in a high percentage of cases, can progress to rheumatic disease, which has been described as polyyarthralgia and/or polyarthritis and can be chronic, flaring, and potentially debilitating (2). In PNAS, Chen et al. (3) present evidence that joint pain and associated symptoms of arthritogenic alphavirus infection (in this case a mouse model of RRV) are strikingly similar to a classical arthritis manifestation, exhibiting cytokine induction profiles reminiscent of rheumatoid arthritis and disruption of osteoblast/osteoclast homeostasis, leading to bone loss.

As a testament to the impact of alphaviral arthritides on humans, the native African names for CHIKV and ONNV mean "that which bends up'" and "weakening of the joints," respectively. Occasionally, large epidemics of alphaviral infectious arthritis occur, such as the 1979–1980 epidemic of RRV in the Pacific Islands, which resulted in more than 60,000 cases, and the recent CHIKV outbreak in Asia, in which as many as 6.5 million people may have been infected (4). This recent outbreak has also led to travel-associated cases in more than 40 countries and establishment of CHIKV and autochthonous spread in Europe (4). Consequently, the recent spread of CHIKV into the eastern Caribbean is a subject of real concern for the United States and Latin and South America. The outbreak in the Caribbean continues to intensify, with a total of 2,024 confirmed cases and more than 7,800 suspected cases as of March 2014 (5). The United States has already had more than 100 travel-associated cases (6), and if CHIKV becomes established in Latin America, it is possible that the first autochthonous cases in the United States will be seen in the next few years. With the abundance of mosquito vectors that are transmission competent for CHIKV in the southern and eastern United States, spread of CHIKV into the country seems inevitable, although the recent history of dengue flavivirus suggests that large-scale epidemics, such as observed in the tropics, are not likely (7). However, currently there are no licensed vaccines for infectious alphaviral arthritides, and due to a limited understanding of the etiology of the arthritic manifestations of disease, few treatment options other than standard pain relief therapy are available (1). Considering the global distribution of these viruses, the severity of impacts on human health, and the potential for additional spread, the development of vaccines and therapeutics for their treatment is critical.

The current work by Chen et al. (3) provides strong evidence that alphaviral arthritis is "real" arthritis. The specific mechanism described in the paper involves virus infection of bone-synthesizing periosteal osteoblast (OB) cells, leading to induction of IL-6 and IL-1β cytokines and monocyte chemotactic protein-1 (MCP-1; CCL-2) monocyte chemoattractive factor and an increase in the ratio of receptor activator of nuclear factor-κB (RANKL) to osteoprotegerin (OPG), which is thought to lead to differentiation of monocytes into bone-resorbing osteoclast (OC) cells (8, 9). In this model, monocytes are recruited to sites of infection through the action of chemokines such as CCL-2 and differentiate into OC-like cells leading to bone erosion (Fig. 1). Furthermore, treatment with an IL-6–neutralizing antibody, similar to an immunomodulation strategy currently undergoing clinical trials for treatment of human rheumatoid arthritis (10), reduced bone loss and reduced RANKL/OPG ratios in sera of mice. Although

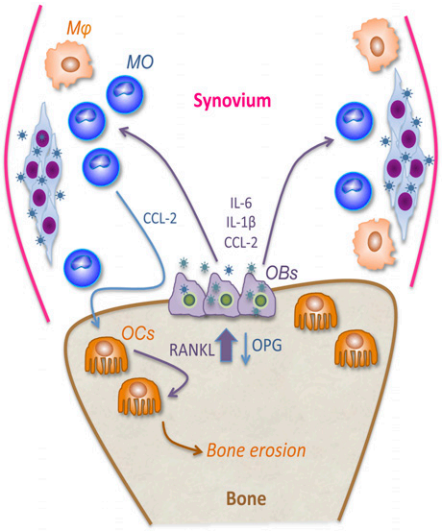


**Fig. 1.** Proposed model for the development of alphaviral arthritis. Virus-infected bone-synthesizing periosteal OB cells in the joint secrete IL-6, IL-1β, and CCL-2 (MCP-1). Monocytes (MOs) are recruited from the synovium to the infected sites by chemoattractive gradients (e.g., CCL-2). An increase in the ratio of RANKL to OPG production by the infected OBs differentiates recruited MOs into bone-resorbing OC cells, leading to bone erosion and arthritis.

the tropism of alphaviruses for osteoblasts and periosteal tissues is well known (11–15), the consequences of this infection to specific disease manifestations have not previously been established in vivo. These results, alongside other recent studies (16, 17), suggest that arthritogenic alphavirus infection of periosteal cells may directly lead to arthritis, which shares multiple features of other human arthritides and may be amenable to similar therapeutic interventions. Furthermore, this work may shed light on arthritis caused by other types of viruses as divergent as dengue virus, enteroviruses, hepatitis C virus, and HIV (18).

Although these studies represent a significant step forward, much like human rheumatoid arthritis, the mechanisms underlying periodic flaring disease observed later after human arthritogenic alphavirus infection (4)

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are yet to be elucidated, and it is unclear whether this involves chronic virus infection and reactivation, host immunopathology, or a combination of both (19, 20). Furthermore, it will be important to determine whether the other arthritogenic alphaviruses elicit a similar pattern of host responses in animal models and humans, although CHIKV does perturb osteoblast RANKL/OPG ratios in vitro (15). It is of interest that most alphaviruses infect periosteum and cultured OBs (10–14), but only a subset cause a prominent arthritis manifestation in humans. Finally, an important component of future studies will be development of a small animal model of chronic, flaring alphavirus arthritis, which will be instrumental for screening new therapeutics and vaccines, and to evaluate the short- and long-term effects of immunomodulation therapies on these arthritides with a unique viral etiology.


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