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INFECTIOUS DISEASES

Targeting T cells to treat Chikungunya virus infections

Chikungunya virus (CHIKV) is a mosquito-transmitted alphavirus that causes fever and joint pain in humans, potentially leading to chronic debilitating arthritis. There are currently no clinically available therapies that effectively prevent or treat CHIKV infection. Two new studies now demonstrate that the FDA-approved agents abatacept and fingolimod (also known as FTY720) relieve arthritis symptoms and reduce disease severity in CHIKV-infected mice.

Previous studies have indicated that chronic CHIKV-induced arthritis is clinically similar to seronegative rheumatoid arthritis (RA). CHIKV-induced joint swelling seems to be an immune-mediated response involving $CD4^+$ T cells, which are the primary mediators of joint inflammation.

Miner *et al.* therefore set out to examine the efficacy of several FDA-approved RA therapies in CHIKV-infected mice. Treatment of mice with abatacept (cytotoxic T lymphocyte antigen 4 (CTLA4)–IgG, which blocks T cell activation) or tofacitinib (a Janus kinase inhibitor) beginning 3 days after CHIKV infection ameliorated foot swelling on day 7 at the point of peak clinical disease without affecting viral RNA levels.

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Next, the authors tested whether a combination of immunomodulatory and antiviral therapies might have greater beneficial effects. Mice treated with abatacept and a neutralizing anti-CHIKV human monoclonal antibody (which had previously been shown to protect against CHIKV-induced lethality in immunocompromised mice) 3 days after CHIKV infection completely abolished foot swelling at day 7. In addition, the anti-CHIKV monoclonal antibodies rapidly eliminated infectious virus particles within 2 days and reduced viral RNA levels in the ankles.

The combination therapy had a greater anti-inflammatory effect than abatacept or the anti-CHIKV monoclonal antibody alone: it reduced the levels of many chemokines and pro-inflammatory cytokines in the joint tissue and leukocyte infiltration into the midfoot joints, also limiting the infiltration of inflammatory cells into the synovial space.

Meanwhile, Teo and colleagues set out to further characterize the pathogenic role of $CD4^+$ T cells during CHIKV infection. First, they transferred primary $CD4^+$ T cells from virus-infected mice or primary $CD4^+$ T cell lines that are specific for dominant viral epitopes into virus-infected T cell receptor-deficient mice, which recapitulated peak joint swelling, vascular leakage, oedema, and inflammation and necrosis of the muscles in the recipient mice.

Given this role of $CD4^+$ T cells in the development of joint inflammation, the authors next assessed the therapeutic potential of clinically approved T cell-suppressive drugs in the treatment of CHIKV infection. Whereas cyclosporin A and rapamycin had no effect on joint inflammation, daily injection of mice with fingolimod (which is a sphingosine 1-phosphate receptor modulator that blocks T cell egress from lymphoid organs and is primarily used for the treatment of multiple sclerosis) reduced joint inflammation in prophylactic and therapeutic regimens.

In addition, fingolimod limited the migration of activated and CHIKV-specific $CD4^+$ T cells into the virus-infected joints, which reduced the severity of joint vascular leakages, oedema in the subcutaneous region, and inflammation and necrosis of muscles.

Together, these studies highlight the potential of targeting T cells in the treatment of CHIKV infection, and the potential of repurposing existing immunomodulatory agents should be further investigated.

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ORIGINAL ARTICLES Miner, J. J. *et al.* Therapy with CTLA4-Ig and an antiviral monoclonal antibody controls chikungunya virus arthritis. *Sci. Transl Med.* **9**, eaah3438 (2017) | Teo, T.-H. *et al.* Fingolimod treatment abrogates chikungunya virus-induced arthralgia. *Sci. Transl Med.* **9**, eaal1333 (2017)