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Cracking the code: ET-1 signaling unlocks new therapies for virus-induced osteoarthritis

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Rheumatic symptoms such as joint inflammation and pain are known features of SARS-CoV-2 infection, though the mechanisms remain unclear. Au and colleagues identified the interaction between the viral spike protein and the endothelin-1 (ET-1) signaling pathway as a cause of osteochondral damage. Their study showed that macitentan, an FDA-approved ET-1 receptor antagonist, reduced joint damage and inflammation in a hamster model, suggesting ET-1 as a potential therapeutic target for viral-induced osteoarthritis (OA).

A number of viruses, including alphaviruses, human immunodeficiency virus, hepatitis viruses, Epstein-Barr virus, herpes simplex virus, cytomegalovirus, and dengue, are known to cause rheumatic disease characterized by joint and muscle inflammation, such as arthritis, myositis, as well as associated pain, including arthralgia and myalgia¹. Among the most prominent are arthritogenic alphaviruses, such as Chikungunya virus and Ross River virus, both of which infect joint and muscle cells, leading to acute and chronic arthritis^{2–4}. Similarly, several clinical studies have linked SARS-CoV-2 infection to musculoskeletal inflammation and pain^{5,6}. Although viral-induced inflammatory arthritis and OA are less commonly reported compared to the overall burden of COVID-19, arthralgia and myalgia remain frequent symptoms⁷. Whether arthritis and myositis are triggered by the direct presence of the virus in joint and muscle tissue remains unknown. Interestingly, no virus was detected in the joint tissues of cadavers from individuals who died of SARS-CoV-2 infection⁸, while viral nucleic acids have been found in the joint of a living patient⁹, suggesting that viral presence in tissues may vary depending on disease stage or individual factors.

Au and colleagues have established a link between SARS-CoV-2 infection and osteochondral damage by identifying a novel mechanism involving the interaction between the viral spike

protein and the host's endothelin-1 (ET-1) signaling pathway¹⁰. ET-1, a potent vasoconstrictor, promotes vascular permeability, enabling the infiltration of inflammatory cells into joint tissues. Using a hamster model, the authors demonstrated that SARS-CoV-2 infection via the ACE2 receptor led to elevated ET-1 levels, increased vascular permeability, and the production of inflammatory cytokines such as TNF, IL-6, and IL-1 β , which contributed to joint inflammation. Additionally, the spike protein was shown to activate TNFSF11 (Tumor Necrosis Factor Ligand Superfamily Member 11) or commonly known as RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand), disrupting the RANKL-OPG (osteoprotegerin) ratio, which are crucial factors in bone remodeling. RANKL promotes osteoclast differentiation and activation, leading to increased bone resorption, while OPG serves as a decoy receptor to neutralize RANKL's effects¹¹. The resulting imbalance in favor of osteoclastogenesis drives bone resorption and joint damage¹¹. The authors also demonstrated that the RBD protein of SARS-CoV-2 increased the gene expression of *EDN1* (Endothelin-1), and its receptors *EDNRA* and *EDNRB* in the endothelial cells, amplifying ET-1 effects triggering the activation of matrix metalloproteinases (MMP1 and MMP13). It is well established that MMP1 helps break down type I collagen and MMP13 breaks down type II collagen^{12–14}. These collective series of events (Fig. 1) contribute to bone loss and cartilage degradation which are both hallmarks of osteoarthritis.

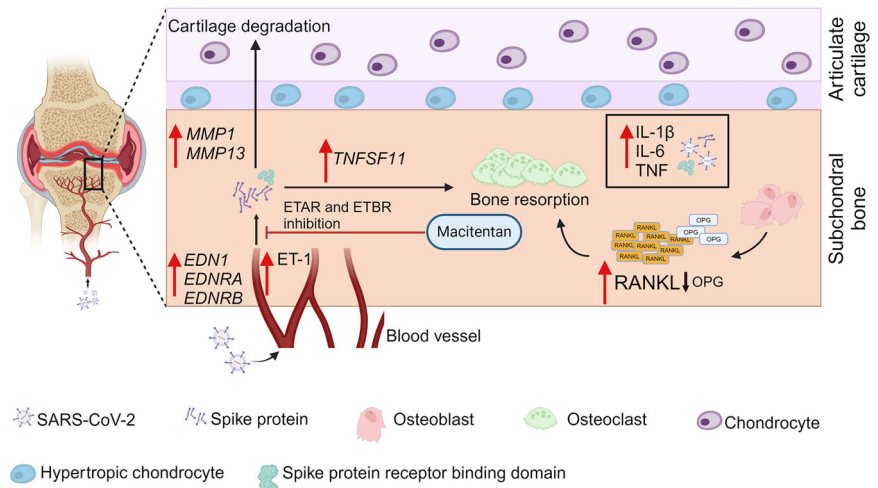
A critical question is whether these mechanistic findings in hamsters are applicable to humans. Computed tomography scans from two COVID-19 patients revealed joint deterioration several months post-infection, including osteoarthritis-like features such as cystic formations, collapse of the subchondral bone plate, and joint space narrowing¹⁰. However, no measurements of ET-1, MMP1, MMP13, RANKL, or OPG were performed in these patients, limiting direct correlation to the hamster model findings¹⁰. Despite this, other studies have reported elevated ET-1 levels in COVID-19 patients^{15,16}, along with altered RANKL/OPG ratios and reduced OPG levels¹⁷, which reflect the mechanistic data in hamsters. To address the lack of direct patient

data, the authors conducted experiments using human endothelial cells (HUVEC) and mesenchymal stem cells-differentiated chondrocytes treated with viral spike protein and ET-1. The results in HUVEC showed that ET-1 significantly lowered OPG and elevated RANKL/OPG levels in human cells, supporting the hamster model observations¹⁰. Whereas in chondrocytes, Au et al. showed that combined treatment with spike protein, neutralizing antibody to S1, and ET-1 resulted in increased expression of *CDKN2B* (coding for p15^{INK4B}) and decreased *CDKN1A* (coding for p21), both key cellular senescence markers. Changes in the level of p15^{INK4B} and p21 levels drive cellular senescence¹⁸ and could lead to the development of senescence-associated secretory phenotype, producing harmful pro-inflammatory signals that worsened joint inflammation and tissue damage. This mirrors what is observed in human cases of post-COVID joint pain¹⁹, linking senescence to long-term musculoskeletal complications²⁰.

Currently, there are no specific treatments for viral arthropathies, though non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, provide symptomatic relief for COVID-19 patients²¹. Au et al., suggest that targeting ET-1 could represent a novel therapeutic approach for mitigating SARS-CoV-2-induced OA. A key strength of this study is the use of macitentan, an FDA-approved drug for pulmonary arterial hypertension (PAH) that functions by blocking endothelin receptors and inhibiting ET-1²². Macitentan treatment reduced vascular permeability, MMP activation, and joint damage in SARS-CoV-2-infected hamsters¹⁰. Additionally, the drug was shown to decrease bone erosion, chondrocyte senescence, and inflammatory cytokine production, ultimately preserving cartilage¹⁰. This discovery suggests that repurposing macitentan could be a potential treatment of SARS-CoV-2-induced OA.

The findings by Au et al., significantly advances our understanding of viral-induced arthritis by uncovering a novel mechanism that bridges the connection between viral infections and arthritis. Notably, there are parallels between their findings and those seen in arthritogenic alphaviruses, where similar yet distinct mechanisms are involved. For example, chikungunya

Fig. 1 | Proposed model for the development of SARS-CoV-2 induced osteoarthritis. SARS-CoV-2 infection induces osteochondral damage by activating the interaction between the viral spike protein and the ET-1 signaling pathway. ET-1 increases vascular permeability, facilitating the infiltration of inflammatory cells into joint tissues and elevating levels of TNF, IL-6, and IL-1 β . The spike protein activates RANKL, disrupting the RANKL-OPG balance, while also upregulating MMP1 and MMP13, leading to collagen breakdown, bone resorption, and cartilage degradation. The effect of ET-1 can be mitigated by using Macitentan, which helps alleviate SARS-CoV-2-induced joint damage.



virus infections are commonly reported to cause chronic joint pain and bone degeneration with evidence that suggests vascular dysfunction may play a role in contributing to these symptoms^{23–25}. Chikungunya virus, like other arthritogenic alphaviruses, specifically targets chondrocytes, and viral replication within these cells leads to chondrocyte damage²⁶. This damage is mediated, in part, by an increase in metalloproteinases—a process also identified in Au et al.'s study, where elevated metalloproteinase levels were detected in SARS-CoV-2-infected tissues. In addition to chondrocyte damage, arthritogenic alphaviruses have been shown to infect osteoblasts, resulting in dysregulation of bone-related molecules, particularly RANKL and OPG^{2,11}. Au et al. similarly observed this dysregulation in SARS-CoV-2 infection, further highlighting the shared pathophysiological mechanisms between these two viruses. Given the comparable effects of chikungunya and SARS-CoV-2 on joint tissue^{2,11,17}, the therapeutic potential of macitentan may extend beyond COVID-19 to other viral-induced arthritic conditions, including chikungunya.

Future research should aim to validate these findings in hamsters in human studies and extend this mechanistic understanding to clinical trials. Trials investigating the long-term effects of ET-1 inhibition, particularly in patients suffering from long-COVID-19 arthritis, will be crucial for determining the therapeutic efficacy of macitentan in mitigating the persistent musculoskeletal symptoms associated with SARS-CoV-2 infection. Furthermore, ET-1's role may not be exclusive to SARS-CoV-2, suggesting its broader relevance in viral arthropathies, thus presenting a promising target for future therapeutic interventions.

Data availability

No datasets were generated or analyzed during the current study.

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BioRender was used to generate Fig. 1.

Author contributions

S.M., W.H.N., and P.C.H.T. wrote and edited the paper. P.C.H.T. prepared Fig. 1.

Competing interests

The authors declare no competing interests.

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