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Author

Zaid, Ali, Sheng, Kuo-Ching, Taylor, Adam, Rulli, Nestor, Herrero, Lara, McNeil, Patrick, Mahalingam, Suresh

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Exacerbation of Alphaviral Arthritis and Myositis in a Mouse Model after Etanercept Treatment is due to Diminished Levels of Interferon α/β

Ali Zaid¹, Kuo-Ching Sheng¹, Adam Taylor¹, Nestor E Rulli¹, Lara J Herrero¹, Patrick McNeil H² and Suresh Mahalingam^{1*}

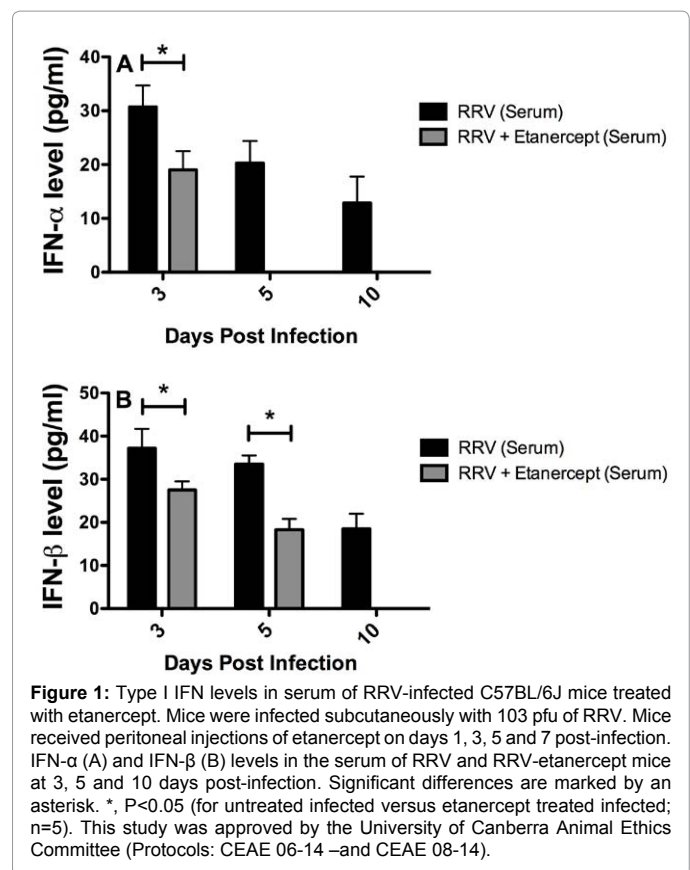
¹Emerging Viruses and Inflammation Research Group, Institute for Glycomics, Griffith University, Gold Coast, Australia

²South Western Sydney Clinical School, University of New South Wales, Sydney, Australia

Little is known about the possible use of TNF- α inhibitors for treating viral arthritis and myositis caused by mosquito-borne arthritogenic alphaviruses such as Ross River virus (RRV), chikungunya virus (CHIKV), and Barmah Forest virus. Emerging alphaviruses such as CHIKV, Mayaro virus and O'nyong-nyong virus are now considered significant public health threats by the World Health Organisation (WHO), with reports of severe cases of debilitating arthritis and arthralgia due to these agents in numerous regions of the world [1]. Although alphavirus-induced arthritis is generally self-limiting, the disease can be severe and the virus can persist and establish chronic infection [1]. For example, Hourau et al. recently showed the persistence of CHIKV antigen in perivascular synovial macrophages in a patient 18 months after infection [2]. At present, there are no alphavirus vaccines or antiviral drugs available for humans. The current treatments available for symptoms caused by alphavirus disease consist of non-steroidal anti-inflammatory drugs such as aspirin or ibuprofen [1].

In recent years we have identified key mechanisms of viral arthritis using our mouse model of alphavirus-induced arthritides and have been investigating ways to reduce joint and muscle inflammation. In this model, macrophages are prominent within the synovial joints and high levels of pro-inflammatory cytokines such as TNF- α and MCP-1 are produced [3]. This is similar to the synovial joints of RRV patients suffering from polyarthritis, in which these soluble factors and macrophages are also prominent. These observations suggest that a considerable immunopathological component is involved in alphavirus-induced arthritis [3]. Targeting specific inflammatory mediators within the joint provides a possible therapeutic approach to alleviate the disease. Indeed, depletion of macrophages by administration of clodronate in mice resulted in marked improvement of the disease. Similarly, the pharmaceutical compound bindarit, an indazole derivative capable of inhibiting MCP-1 production and monocyte recruitment, has a beneficial therapeutic effect on alphavirus disease in mice [4,5]. In our recent work [6], we determined whether inhibiting TNF- α in vivo could ameliorate the alphaviral arthritis, based on the therapeutic efficacy of this treatment in autoimmune diseases. Surprisingly, we found that treating alphavirus-infected mice with etanercept exacerbated muscle and joint inflammation, with increased cellular infiltration in the synovium and muscle fibres [6]. In addition, viral titres were higher in etanercept treated mice, and this associated with high morbidity [6]. These results indicated that TNF- α has a protective role during alphavirus infection in mice and highlights the important role of this cytokine in antiviral immune responses. The differential effects of anti-TNF- α treatment in autoimmune inflammation and viral arthritis reflects the pleiotropic nature of this cytokine: while TNF- α is pro-inflammatory by inducing cell activation, apoptosis and tissue destruction, it is also a critical activator of signalling pathways, such as NF κ B and MAPK, that are indispensable for production of various cytokines and chemokines to achieve immune competency [7]. To this end, TNF- α has been linked to the action of a critical class of cytokines, type I interferons (IFNs) [7]. TNF- α can stimulate IFN- β production and initiate an autocrine loop that sustains IFN-induced gene expression [7]. Furthermore, TNF- α

synergises with IFN- β to enhance chemokine production and the antiviral response [7]. Type I IFNs potentially inhibit alphavirus replication and have been proposed as a potential treatment. Based on the inter-relationship between TNF- α and type I IFNs, we hypothesized that the exacerbation of alphaviral arthritis by etanercept was due to alterations in the level of type I IFNs. Indeed, IFN- α and IFN- β levels were greatly reduced or undetectable in mice infected with RRV and treated with etanercept (Figure 1A and 1B). These results suggest that anti-TNF- α dampens host anti-viral immunity by inhibiting the production of type



*Corresponding author: Suresh Mahalingam, Emerging Viruses and Inflammation Research Group, Institute for Glycomics, Griffith University (Gold Coast Campus), Queensland 4222, Australia, Tel: +61 7 5552 7178; Fax: +61 7 5552 8098; E-mail: s.mahalingam@griffith.edu.au

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I IFN. The potency of etanercept in this model is, therefore, likely due to dual inhibition of the synergistic partners TNF- α and type I IFN.

Side effects of etanercept were officially reported by the US health authorities, following the death of some etanercept treated patients as a result of severe sepsis [8]. Etanercept treatment has also been associated with severe viral respiratory tract infections in humans [9]. In addition, patients receiving anti-TNF- α therapy may be associated with an increased risk of viral infections like human immunodeficiency virus, varicella zoster virus, Epstein-Barr virus, cytomegalovirus and papillomavirus [9,10]. Reactivation of latent infection with *M. tuberculosis* has been reported following anti-TNF- α treatment, and patients contemplating anti-TNF- α therapy should be screened for latent infection before therapy [9]. We suggest that RA patients receiving anti-TNF- α drugs would be more susceptible to alphavirus infection, and clinicians must be particularly aware of the possibility of viral infection as a cause of disease exacerbation in RA patients receiving anti-TNF- α drugs, particularly in areas where arthrogenic alphaviruses are endemic. Anti-TNF- α therapy should be avoided for the clinical treatment of alphavirus-induced arthritis as it may dampen the anti-viral activity of type I IFNs that are essential for viral clearance. In conclusion, patients presenting with arthritic symptoms should be screened for alphavirus serum antibodies as a precaution before being prescribed anti-TNF- α therapy for RA.

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