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MINI REVIEW

The Role of Interleukin-37 in Inflammation: Suppression or Promotion?

Liping Ding, Xiaoping Hong and Dongzhou Liu*

Department of Rheumatology and Immunology, Shenzhen People's Hospital, The Second Clinical Medical College, Jinan University, Shenzhen, China

***Corresponding author:** *Dongzhou Liu, Department of Rheumatology and Immunology, Shenzhen People's Hospital, The Second Clinical Medical College, Jinan University, Shenzhen, China, E-mail: liu_dz2001@sina.com*

We read with great interest the paper presented in the current issue of the *Journal of innate immunity by* Schauer, et al. [1] showing the pathogenic role of Interleukin-37 (IL-37) in the murine model of *Streptococcus pneumoniae* pneumonia. This study found that recruitment of alveolar macrophages and neutrophils was markedly increased in the mice transgenic for human IL-37b (IL-37tg) with heavier pneumococcal burden, resulting in necrotizing pneumonia with augmented death of infiltrating neutrophils, and leading to enhanced inflammation, tissue damage, and mortality. However, several published studies displayed IL-37tg mice had less severe inflammation in models of endotoxin shock, colitis, obesity-induced inflammation and myocardial inflammatory [2-5]. The authors argued that it is mainly due to the core components of a successful inflammatory response to pneumococcal pneumonia, which lead to increased inflammation, tissue damage, and mortality and is modulated by IL-37 cytokine [1].

However, recent studies have suggested that IL-37 is a potent inhibitor of innate immunity by shifting the cytokine equilibrium away from excessive inflammation. *In vivo*, IL-37 exhibited anti-inflammatory activity in murine models of dextran sulfate sodium-induced colitis, monosodium urate crystal-induced inflammation, psoriasis, myocarditis, rheumatoid arthritis and airway inflammation [6-11]. IL-37 not only has anti-inflammatory effects, but also induces marked metabolic changes with higher levels of muscle AMPK, greater rates of oxygen consumption, and increased oxidative phosphorylation both in the context of inflammation-induced fatigue and in healthy mice [12]. In addition, expression of human IL-37 in mice could protect cardiomyocytes from apoptosis and suppress the migration ability of neutrophils in myocardial ischaemia/reperfusion injury condition [13]. Administration of IL-37 to the mice which subjected to endotoxin or high fat diet could attenuate aortic valve thickening and control the progression of calcific aortic valve disease [14]. Previous studies have shown that IL-37 has therapeutic potential for these mouse models of human disease.

IL-37 has been found to increase and restrain the pro-inflammatory cytokine production in various diseases associated with inflammation, including Tuberculosis, Behçet's disease, Acute coronary syndrome, Graves' disease, Ankylosing Spondylitis and Erosive osteoarthritis [15-20]. These findings further suggest an immunosuppressive role of IL-37 in the pathogenesis of autoimmune inflammation by downregulating pro-inflammatory cytokines. Proteomic and transcriptomic investigations revealed that the anti-inflammatory properties of IL-37 require the receptors IL-18Rα and IL-1R8 (SIGIRR) to harness the signaling molecules Mer, PTEN, STAT3 and p62(dok), and further suppress the kinases Fyn and TAK1 and the transcription factor NF-κB, as well as MAPK [21].

In conclusion, we agree with Schauer's statement that IL-37tg mice could develop excessive inflammation and tissue damage when faced with *S. pneumoniae* infection. However, we believe that IL-37, as anti-inflammation cytokine, is involved in various diseases with inflammation, at least in humans. As autoimmune and infectious diseases share common characteristics in the

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inflammatory responses, improved understanding of the role of IL-37 in humans with autoimmune diseases or infections may have significant implications for identifying IL-37 as a biomarker for disease progress and therapeutic target.

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