

## Implications of IL-6 Targeting Therapy for Sepsis

Sujin Kang<sup>1,2</sup>, Toshio Tanaka<sup>1,2</sup>, Kazuya Masuda<sup>3</sup> and Tadamitsu Kishimoto<sup>3\*</sup>

<sup>1</sup>Department of Clinical Application of Biologics, Osaka University Graduate School of Medicine, 2-2 Yamada-oka, Suita, Osaka 565-0871, Japan

<sup>2</sup>Department of Respiratory Medicine, Allergy and Rheumatic Diseases, Osaka University Graduate School of Medicine, 2-2 Yamada-oka, Suita, Osaka 565-0871, Japan

<sup>3</sup>Laboratory of Immune Regulation, WPI-Immunology Frontier Research Center, Osaka University, 3-1 Yamada-oka, Suita, Osaka 565-0871, Japan

\*Corresponding author: Tadamitsu Kishimoto, Department of Clinical Application of Biologics, Osaka University Graduate School of Medicine, 2-2 Yamada-oka, Suita, Osaka 565-0871, Japan, Tel: +81-6-6879-3833; E-mail: [kishimoto@ifrec.osaka-u.ac.jp](mailto:kishimoto@ifrec.osaka-u.ac.jp)

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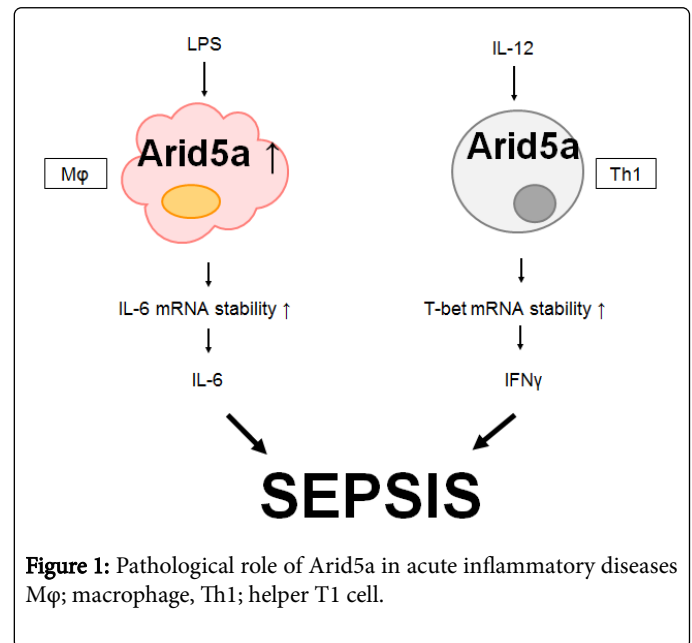
### Commentary

As previously reviewed by Kang et al. [1], dysregulated persistent expression of IL-6 leads to chronic inflammatory diseases, therefore, IL-6 targeting therapy is useful for the treatment of chronic diseases. Moreover, accumulated evidence suggests that IL-6 is a potential target molecule for the treatment of severe inflammatory response syndrome (SIRS) including sepsis [2]. However, the molecular mechanisms through which IL-6 is excessively or persistently produced remain unknown. In this commentary, we highlight on the involvement of a novel RNA-binding molecule (Arid5a) on dysregulated IL-6 synthesis.

Cytokines are small molecules that mediate cell to cell communication in immune responses and also regulate migration of immune cells at the site of infection, trauma and tissue injury [3]. In general, an appropriate regulation of cytokines production is an important event in host defenses and maintenance of immune homeostasis. However, exaggerative elevation of cytokine production might lead to the onset or development of acute inflammatory diseases. Sepsis is severe systemic inflammatory response upon infection, leading to excessive pro-inflammatory cytokine production such as IL-6, TNF $\alpha$  and IFN $\gamma$  [4,5]. Upon infection, IL-6 and TNF $\alpha$  are highly expressed by innate immune cells including macrophages and dendritic cells, whereas IFN $\gamma$  is produced by IL-12-derived T helper type 1 (Th1) cells. Recently, genetic contributions of IL-6 has been also identified that single nucleotide polymorphism (SNP) at IL-6 promoter has been related to IL-6 production and associated with the risk of sepsis [6]. Collectively, these findings suggests the therapeutic potential of blocking of these cytokines in development of sepsis.

Interleukin-6 (IL-6), which is originally identified as B cell stimulatory factor-2 (BSF-2), plays an important role in early phase of acute immune responses and hematopoiesis by activating lymphocytes, hepatocytes and hematopoietic cells to protect the body against invasion of pathogens. By contrast, persistent production of IL-6 leads to development of various chronic diseases, including rheumatoid arthritis, juvenile idiopathic arthritis and Castleman disease [7,8].

On the basis of the pathological involvement of IL-6 in chronic diseases, tocilizumab, a humanized anti-IL-6 receptor antibody was developed and various clinical trials proved its outstanding efficacy for those chronic immune disorders. This biologics is also expected to become a novel therapeutic drug for severe inflammatory response syndrome (SIRS) including sepsis, since extremely high level of IL-6 is well documented to be associated with severity and prognosis of sepsis [2]. Moreover, tocilizumab is shown to be very efficacious for cytokine release syndrome (CRS), accompanied by T-cell engaged therapy.



**Figure 1:** Pathological role of Arid5a in acute inflammatory diseases M $\phi$ ; macrophage, Th1; helper T1 cell.

IL-6 interacts with two different receptors, namely, IL-6 receptor (IL-6R) and the signal-transducing receptor subunit gp130. IL-6R exists in two forms, an 80-kDa transmembrane form and a 50-55 kDa soluble form (sIL-6R). Transmembrane type of IL-6R interacts with gp130 and triggers a downstream signals upon binding of IL-6, which referred as “classical IL-6 signaling pathway”. sIL-6R is present in human serum, and also binds to IL-6; this complex transduces the IL-6 signal on gp130 expressing cells, which is known as “trans IL-6 signaling pathway” [9,10]. IL-6 stimulation activates gp130 downstream signaling molecules, that is, the Janus kinase (JAK)-Signal transducers and activator of transcription 3 (STAT3) pathway and JAK-SH2 domain containing protein tyrosine phosphatase 2 (SHP2)-mitogen-activated protein kinase (MAPK) pathway. During infection or tissue injury, IL-6 is synthesized very rapidly, resulting in elimination of invading pathogens.

Upon inflammatory stimuli, transcription of IL-6 are regulated by several factors such as nuclear factor kappa B (NF- $\kappa$ B), specificity protein 1 (SP1), nuclear factor IL-6 (NF-IL6), activator protein 1 (AP1) and interferon regulatory factor 1 (IRF-1). Recently, our group and the Akira group clarified the post-transcriptional regulatory mechanisms of IL-6 mRNA by two counteractive molecules [11,12]. Akira et al. found that Regnase-1, a kind of nuclease, which binds at the site 3'-untranslated region (3'-UTR) and destabilizes of IL-6 mRNA. By LPS stimulation, Regnase-1 is phosphorylated following then get

degradation by ubiquitination. This protein also acts as a negative regulator by binding to the stem loop site of the 3'-UTR of Regnase-1 mRNA itself.

Our group identified that Arid5a, which is a counteractive partner to Regnase-1, is a stabilizer in terms of binding to the 3'-UTR of IL-6 mRNA [5]. The expression of Arid5a is quickly induced in macrophages upon LPS stimulation (Figure 1). As expected, genetic deletion of Arid5a in mice displayed significantly less production of IL-6 in a LPS-induced endotoxin shock model. Collectively, these findings strongly suggest that modulation of IL-6 post-transcription is related to pathogenesis of sepsis. Additionally, we found the significant involvement of Arid5a in the differentiation of naïve helper T (Th) cells into Th17 cells in a murine experimental autoimmune encephalomyelitis (EAE) model, by controlling by stability of STAT3 mRNA [13].

More recently, we also observed not only therapeutic effects of blockade of two different cytokines, IL-6 and IFN $\gamma$ , against sepsis development, but also the novel function of Arid5a in the development of naïve T cells into Th1 cells by stabilizing T-bet mRNA [14]. Arid5a-deficient mice in *Propionibacterium acnes*-primed endotoxin shock model, which elicit Th1 responses, showed lower levels of IFN $\gamma$ , IL-6 and TNF $\alpha$ , with higher survival rate. These findings implicate that both IL-6 and IL-6 mRNA regulator, Arid5a are target molecules for the treatment of septic shock [15].

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