Tang Prize Grant Final Report

Title: Efficacy of Anti-IL-6 receptor (Tocilizumab) treatment in several types of Cytokine Release Syndrome

Interleukin-6 (IL-6) is an important cytokine in the early phase of acute immune responses, by which activation of lymphocytes, hematopoietic cells, and vascular endothelial cells protect the body against the invasion of pathogens. By contrast, persistent production of IL-6 leads to the development of various chronic diseases such as rheumatoid arthritis (RA), and juvenile idiopathic arthritis (JIA). Regarding the significance of IL-6 in the pathogenesis of chronic diseases, tocilizumab, a humanized anti-IL-6 receptor antibody successfully proved its outstanding efficacy against those chronic immune disorders. However, a high level of IL-6 expression has also been revealed in the sera of patients from systemic inflammatory responses syndrome (SIRS) and cytokine release syndrome (CRS).

Protection against endothelial damage is recognized as a frontline approach to preventing the progression of CRS. Previous our study demonstrated that endothelial IL-6 trans-signaling contributed CRS progression and blockade of IL-6 receptor signaling showed clinically beneficial effects in severe COVID-19 patients by reduction of serum PAI-1 levels (Kang S et al, ***PNAS***, 2020). In addition, the efficacy of the anti-IL-6R antibody, tocilizumab has been first approved by FDA for infectious diseases, severe COVID-19 (Kishimoto T and Kang S, ***Ann Rev Immunol***, 2022). Accumulating evidence has demonstrated that IL-6 promotes vascular endothelial damage during CRS, although the molecular mechanisms remain to be fully elucidated. Targeting IL-6 receptor signaling delays CRS progression; however, current options are limited by persistent inhibition of the immune system. By the research supporting grant, we identified that endothelial IL-6 trans-signaling promoted vascular damage and inflammatory responses via hypoxia-inducible factor-1α (HIF1α)–induced glycolysis by bulk RNA-sequencing analysis of IL-6R (IL-6 receptor) trans-signaling induced HUVECs. Using pharmacological inhibitors targeting HIF1α activity or mice with the genetic ablation of gp130 in the endothelium, we found that inhibition of IL-6R–HIF1α signaling in endothelial cells protected against vascular injury caused by septic damage and provided survival benefit in a mouse model of sepsis. However, tocilizumab treatment has a higher risk of bacterial infection. In this context, it is difficult to use for therapeutic purposes such as infectious diseases because of its half-life to sustain for the long term. Next, we developed a short half-life anti-IL-6R antibody (silent anti-IL-6R antibody) and found that it was highly effective at augmenting survival for sepsis and severe burn by strengthening the endothelial glycocalyx and reducing cytokine storm, and vascular leakage with inhibition of secondary infection. Together, our data advance the role of endothelial

IL-6 trans-signaling in the progression of CRS and indicate a potential therapeutic approach for burns and sepsis (Kang et al, ***PNAS***, 2024) (Figure 1).

References

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Figure 1. Generation of a next-generation antibody for infectious diseases.

