Biologics in *Staphylococcus aureus* Arthritis

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i föreläsningssalen våning 3, Guldhedsgatan 10A, Göteborg, fredagen den 29 april, 2016, kl. 09:00

av

Abukar Ali

Avhandlingen baseras på följande delarbeten:

I. Ali A, Zhu X, Kwiecinski J, Gjertsson I, Lindholm C, Iwakura Y, Wang X, Lycke N, Josefsson E, Pullerits R, Jin T. Antibiotic-killed *Staphylococcus aureus* induces destructive arthritis in mice. *Arthritis Rheumatol,* 2015; 67:107-116.

II. Ali A, Welin A, Schwarze JC, Svensson MN, Na M, Jarneborn A, Magnusson M, Mohammad M, Kwiecinski J, Josefsson E, Bylund J, Pullerits R, Jin T. CTLA4 Immunoglobulin but Not Anti-Tumor Necrosis Factor Therapy Promotes Staphylococcal Septic Arthritis in Mice. *J Infect Dis*, 2015; 212: 1308-1316.

III. Ali A, Na M, Svensson MN, Magnusson M, Welin A, Schwarze JC, Mohammad M, Josefsson E, Pullerits R, Jin T. IL-1 Receptor Antagonist Treatment Aggravates Staphylococcal Septic Arthritis and Sepsis in Mice. *PLoS One*, 2015; 10(7)

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ABSTRACT

The emergence of new type of drugs known as biologics has led to rapid disease improvements in many autoimmune arthritic patients. Nevertheless, most of these biologics are immunomodulators that may consequently increase the susceptibility of patients towards infections, such as septic arthritis. Septic arthritis is still considered a major public health challenge due to its rapidly progressive disease character with poor prognosis regarding joint functions. It is mainly caused by *Staphylococcus aureus* and despite optimal antibiotic treatment, nearly half of patients have permanent joint dysfunction.

The main aim of this thesis was to investigate the inflammatory response of the host to living as well as antibiotics-killed *S. aureus* and to study the effect of biologics on the course of staphylococcal infections. The role of host inflammatory response on post-infectious joint dysfunction using antibiotic-killed *S. aureus* was the subject of Paper I of this thesis. The main focus of Paper II and III were to study the effects of different biologics treatments on *S. aureus* induced septic arthritis and sepsis.

We demonstrated that antibiotic-killed *S. aureus* is capable of inducing and maintaining destructive arthritis. By using different knockout mice, we showed that this type of arthritis was mediated through TLR-2, TNFR1 and RAGE receptors. Furthermore, we found that insoluble cell debris was a key initiator of this type of arthritis. Finally, anti-TNF therapy attenuated the arthritis caused by antibiotic-killed *S. aureus*.

All the biologic treatments tested (including anti-TNF therapy, CTLA4-Ig and IL-1 Ra) aggravated *S. aureus* infections but had different clinical manifestations. Both CTLA4-Ig and IL-1 Ra therapy significantly increased the susceptibility to *S. aureus* induced septic arthritis in mice. Anti-TNF therapy on the other hand resulted in more severe weight loss and impaired the bacterial clearance ability of the host.

In conclusion, antibiotic-killed *S. aureus* induced chronic destructive arthritis and anti-TNF therapy attenuated this type of joint inflammation. In the living *S. aureus* induced septic arthritis, all tested biologics complicated the disease course. Therefore, the potential dangers associated with biologics should be taken into account and patients with high risk of *S. aureus* bacteremia might be considered to refrain from them.

Keywords: *Staphylococcus aureus,* CTLA4-Ig, IL-1 Ra, anti-TNF therapy, mouse, septic arthritis

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