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Lipoproteins in *Staphylococcus aureus* infections

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg

Tisdagen den 29 september 2020, klockan 09:00

av

Majd Mohammad

Fakultetsopponent:

Professor Andreas Peschel

University of Tübingen, Germany

Avhandlingen baseras på följande delarbeten:

I. **Mohammad M**, Nguyen M-T, Engdahl C, Na M, Jarneborn A, Hu Z, Karlsson A, Pullerits R, Ali A, Götz F, Jin T. The YIN and YANG of lipoproteins in developing and preventing infectious arthritis by *Staphylococcus aureus*. *PLoS Pathogens*, 2019; 15(6): e1007877.

II. **Mohammad M**, Hu Z, Ali A, Kopparapu PK, Na M, Jarneborn A, Stroparo MN, Nguyen M-T, Karlsson A, Götz F, Pullerits R, Jin T. The role of *Staphylococcus aureus* lipoproteins in hematogenous septic arthritis. *Scientific Reports*, 2020; 10(1):7936.

III. **Mohammad M**, Na M, Hu Z, Nguyen M-T, Kopparapu PK, Jarneborn A, Karlsson A, Ali A, Pullerits R, Götz F, Jin T. The role of *Staphylococcus aureus* lipoproteins in skin infection. *Under revision*

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Lipoproteins in *Staphylococcus aureus* infections

Majd Mohammad

Department of Rheumatology and Inflammation Research
Institute of Medicine, Sahlgrenska Academy at University of Gothenburg, Sweden, 2020.

Abstract

Staphylococcus aureus (*S. aureus*) infections remain a major challenge for the healthcare system, and new treatment options are highly demanded. *S. aureus* is a pathogenic microorganism, responsible for a broad range of clinical infections in humans. Septic arthritis, a debilitating joint disease, is mainly due to *S. aureus*. Furthermore, the majority of skin and soft tissue infections are also caused by *S. aureus*. *S. aureus* expresses multiple bacterial molecules, including bacterial lipoproteins (Lpps), which play a role in the disease pathogenesis. *S. aureus* Lpps, the predominant ligands for TLR2, are important for bacterial survival due to their role in maintaining the metabolic activity of the bacteria. So far, their role in different staphylococcal infections have not been fully defined.

The aim of this thesis was to explore the role of *S. aureus* Lpp in the mouse models for septic arthritis and skin infection. The severity of septic arthritis and skin inflammation/infection as well as the molecular and cellular response of the host upon *S. aureus* Lpp exposure was the main focus of the thesis.

S. aureus Lpp, injected intra-articularly into murine knee joints, induced chronic macroscopic arthritis of a destructive character, which was mediated by monocytes/macrophages via TLR2. However, co-injection of purified *S. aureus* Lpp with *S. aureus* into mouse knees resulted in increased bacterial elimination. Mice intravenously infected with the *S. aureus* Lpp-expressing Newman parental strain, had increased mortality and weight reduction as well as impaired bacterial clearance in kidneys independent of TLR2 compared to those mice infected with Lpp-deficient strain. However, Lpp expression had no significant impact on the severity of bone destruction. Finally, in a skin infection model, expression of Lpp in *S. aureus* was associated with an enhanced inflammatory response and increased bacterial burden in the local infection site.

In conclusion, *S. aureus* Lpps play differential roles depending on the route of infection. In the case of locally-induced arthritis, *S. aureus* Lpps play a dual role – on the one hand, Lpps contribute to joint inflammation and damage; on the other hand, Lpps elicit strong innate immune responses, resulting in efficient bacterial elimination. In haematogenous septic arthritis, Lpps have a limited impact on arthritis development. Finally, in the skin infection model, *S. aureus* Lpps contribute to local skin inflammation and enhance skin abscess formation.

Keywords: *Staphylococcus aureus*; lipoproteins; TLR2; septic arthritis; skin infection; mouse

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