Göteborg, 2024

Impact of JAK-inhibition on infections

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Föreläsningssalen, Guldhedsgatan 10A, den 28:e november 2024, klockan 9:00.

av **Anders Jarneborn**

Fakultetsopponent:
Keira Melican, PhD, Associate professor
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Avhandlingen baseras på följande delarbeten

I. **Jarneborn, A**.; Mohammad, M.; Engdahl, C.; Hu, Z.; Na, M.; Ali, A.; Jin, T. Tofacitinib treatment aggravates Staphylococcus aureus septic arthritis, but attenuates sepsis and enterotoxin induced shock in mice. Sci Rep 2020, 10, 10891.

II. Krzyzowska, M.; **Jarneborn, A**.; Thorn, K.; Eriksson, K.; Jin, T. Tofacitinib Treatment in Primary Herpes Simplex Encephalitis Interferes With Antiviral Response. *J Infect Dis* **2022**, *225*, 1545-1553. (M. K. and A. J. contributed equally.)

III. **Jarneborn, A**.; Hu, Z.; Deshmukh, M.; Kopparapu, P.K.; Jin, T. Tofacitinib Treatment Suppresses CD4+ T-Cell Activation and Th1 Response, Contributing to Protection against Staphylococcal Toxic Shock. Int J Mol Sci 2024, 25.

SAHLGRENSKA AKADEMIN
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Abstract

With the growing arsenal of treatment options for immune modulation come great opportunities to help patients. However, tampering with immune cells and their various mediators is also associated with risk, including increased susceptibility to and severity of infections. In addition, some infectious diseases are associated with such a strong or misguided immune response that the mechanisms meant to protect cause harm. In such cases, immune modulation might have a protective effect in an infectious setting. The aim of this thesis is to explore the effect of a class of drugs called Janus kinase-inhibitors in context of infections. These drugs are used to treat various immune-related diseases, with rheumatoid arthritis being the most prominent. In this thesis we focus on the first drug approved for this diagnosis, tofacitinib. In **paper I** we examined the effect of tofacitinib treatment on bacterial infections caused by *Staphylococcus aureus* (*S. aureus*). We found that treatment with tofacitinib aggravates the bone erosions caused by *S. aureus* septic arthritis. On the other hand, with a higher dose of bacteria, which induces lethal bacteremia, tofacitinib has a protective effect. Further study of toxic shock induced by *S. aureus* derived superantigen toxin toxic shock syndrome toxin-1 (TSST-1) and endotoxin, revealed a potent effect, with the majority of treated mice being rescued from the highly lethal shock. In **paper II** we examined the effect of tofacitinib in a mouse model of herpes encephalitis caused by herpes simplex virus 1. Here we showed that mice treated with tofacitinib exhibited worse clinical symptoms and higher viral load in the brain. This was accompanied by less expression of specific antiviral cytokines and chemokines, and higher expression of more general pro-inflammatory mediators. Furthermore, tofacitinib affects polarization of microglia and infiltrating monocytes, key players in the defense against CNS-infection, favoring a M2 phenotype over M1. In **paper III** we further studied the effect of tofacitinib on T-cells in the TSST-1 and endotoxin-induced shock mouse model, to better understand the protective effect of the drug. We showed that tofacitinib dampens the activation of T-cells and leads to a cytokine environment limiting a Th1 response. In conclusion, we show the dual effect of immune manipulation with tofacitinib in the context of infection, with both detrimental and possible positive effects depending on the setting.

Keywords: *Staphylococcus aureus*, herpes simplex virus 1, septic arthritis, toxic shock syndrome toxin 1, tofacitinib, mice.

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