

Neoehrlichiosis - Latent infection of endothelium and immune defense

Akademisk avhandling

Som för avläggande av medicine doktorexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligens försvaras i föreläsningssalen, Klinisk Mikrobiologi, Guldhedsgatan 10A, 413 46 Göteborg, fredagen den 8 december 2023, klockan 09:00

av Linda Wass

Fakultetsopponent:

Docent, universitetslektor, ÖL Kristina Persson
Lunds Universitet, Sverige

Avhandlingen baseras på följande delarbeten

- I. Wass L, Grankvist A, Mattsson M, Gustafsson H, Krogfelt K, Olsen B, Nilsson K, Mårtensson A, Quarsten H, Henningson AJ, Wennerås C. **Serological reactivity to *Anaplasma phagocytophilum* in neoehrlichiosis patients.** Eur J Clin Microbiol Infect Dis. 2018 Sep;37(9):1673-1678.
- II. Wass L*, Grankvist A*, Bell-Sakyi L, Bergström M, Ulfhammer E, Lingblom C, Wennerås C. **Cultivation of the causative agent of human neoehrlichiosis from clinical isolates identifies vascular endothelium as a target of infection.** Emerg Microbes Infect. 2019;8(1):413-425. *The authors contributed equally
- III. Wass L, Quarsten H, Lindgren PE, Forsberg P, Skoog E, Nilsson K, Lingblom C, Wennerås C. **Cytokine responses of immunosuppressed and immunocompetent patients with *Neoehrlichia mikurensis* infection.** Med Microbiol Immunol. 2022 Jun;211(2-3):133-141.
- IV. Wass L, Lingblom C, Jaén-Luchoro D, Brundin S, Lewerin C, Wennerås C. ***Neoehrlichia mikurensis* causes latent persistent infections that reactivate when B-cells are suppressed in patients with B-cell lymphomas**(in manuscript).

**SAHLGRENKA AKADEMIN
INSTITUTIONEN FÖR BIOMEDICIN**



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Linda Wass

Avdelningen för Infektionssjukdomar, Institutionen för Biomedicin, Sahlgrenska akademien, Göteborgs universitet, Sverige, 2023.

Abstract

This thesis is a study of the tick-borne pathogen *Neoehrlichia* (*N.*) *mikurensis* that causes the infectious disease neoehrlichiosis in humans. The disease affects both individuals with competent and suppressed immune defense with the majority of the affected being immunosuppressed. The most common symptoms of neoehrlichiosis are recurrent fever, nightly sweats as well as muscle and joint pain. The most prominent clinical features are vascular events with thrombosis and arteritis. The aims of this thesis were to identify the target cells of the infection and get a deeper understanding of the immune responses evoked by *N. mikurensis*. In the first paper, it is described how some patients diagnosed with neoehrlichiosis also have antibodies targeted against another member of the *Anaplasmataceae* family, *Anaplasma phagocytophilum*. This can lead to patients with neoehrlichiosis mistakenly being diagnosed with anaplasmosis. In the second paper we describe for the first time that *N. mikurensis* can be cultivated and propagated both in tick cells and human endothelial cells. *N. mikurensis* was also demonstrated inside of circulating endothelial cells isolated from the blood of patients with neoehrlichiosis. These findings indicate that endothelial cells are a target cell of the infection, which could also explain the many vascular events affecting patients. In paper III we show that immunosuppressed patients with *N. mikurensis* infection had increased serum levels of cytokines involved in B cell responses (CXCL13 and B-cell activating factor), the pro-inflammatory cytokine CXCL10 as well as cytokines associated with growth of blood vessels (vascular endothelial growth factor and fibroblast growth factor basic). We also show the importance of confirming results obtained with multiplex cytokine assays with single plex tests. In the last paper IV, we lend support to the hypothesis that *N. mikurensis* infections in humans are latent infections that can reactivate when B-cell responses are suppressed in patients with B-cell lymphomas. Out of 97 patients treated with anti-CD20 antibody therapy, 8 % had a latent *N. mikurensis* infection, it was only the patients with latent infection that had T cells specific for *N. mikurensis*. These T cells were of the $\gamma\delta$, T-helper 1 and cytotoxic T lymphocyte types and expressed the cytolytic protein perforin. This work and future *N. mikurensis* projects will lead to a greater understanding of the infectious disease neoehrlichiosis.

Keywords: *Neoehrlichia mikurensis*, neoehrlichiosis, human, infectious disease, endothelial cell, T cell