

Effects of dietary fatty acids on the immune system

Akademisk avhandling

Som för avläggande av medicine doktorexamen vid Sahlgrenska akademien vid Göteborgs universitet kommer att offentligens försvaras i hörsal Europa, Konferenscentrum Wallenberg, Medicinargatan 20 C, Göteborg
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Avhandlingen baseras på följande arbeten:

- I. **Dietary Polyunsaturated Fatty Acids Increase Survival and Decrease Bacterial Load during Septic *Staphylococcus aureus* Infection and Improve Neutrophil Function in Mice.**
Svahn, S.L.*, Grahnmö, L.*, Pálsdóttir, V., Nookaew, I., Wendt, K., Gabrielsson, B., Schéle, E., Benrick, A., Andersson, N., Nilsson, S., Johansson, M.E. and Jansson, J-O. *Infection and Immunity* 2015 Feb; 83(2): 514-21.
- II. **The Impact of Dietary Fat Composition on the Transcriptomes of Six Tissues Reveals Specific Regulation of Immune Related Genes.**
Svahn, S.L.*, Våremo, L.*, Gabrielsson, B., Peris, E., Nookaew, I., Grahnmö, L., Sandberg, A-S., Wernstedt Asterholm, I., Jansson, J-O., Nielsen, J. and Johansson, M.E. *Inskickat till tidskrift*.
- III. **Dietary Polyunsaturated Fatty Acids lead to Increased G-CSF and Subsequent Neutrophil Expansion.**
Svahn, S.L., Ulleryd, M.A., Nookaew, I., Osla, V., Beckman, F., Nilsson, S., Karlsson, A., Jansson, J-O. and Johansson, M.E. *I manuskriptform*.
- IV. **Dietary Omega-3 Fatty Acids Increase Survival and Decrease Bacterial Load in Mice Subjected to *S. aureus*-induced Sepsis.**
Svahn, S.L., Ulleryd, M.A., Grahnmö, L., Ståhlman, M., Borén, J., Nilsson, S., Jansson, J-O. and Johansson, M.E. *Under revision*.

*Författarna bidrog lika



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Effects of dietary fatty acids on the immune system

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Abstract

Sepsis is a deadly disease with an increasing incidence worldwide. Today, antimicrobials are the only effective pharmacological treatment. At the same time, bacteria, the pathogens behind most cases of sepsis, are becoming more and more resistant to our available antibiotics. A considerable amount of time, effort and money has been spent into finding new drug-candidates for treating sepsis. To date, none has succeeded in clinical trials. Dietary fatty acids affect the immune system. Saturated fatty acids (SFAs) increase the risk for cardiovascular diseases and promote low-grade inflammation, whereas polyunsaturated fatty acids (PUFAs) are beneficial for patients with rheumatoid arthritis and atherosclerosis, being anti-inflammatory. In this thesis, we investigated the effects of dietary fatty acids on the immune system and survival in *S. aureus*-induced sepsis in mice.

Following 8 week of either low fat diet (LFD), high fat diet (HFD) rich in SFAs (HFD-S) or HFD rich in PUFAs (HFD-P) mice were inoculated with *S. aureus* to induce sepsis or investigated for mechanistic studies. Mice fed HFD-P had a better survival in sepsis and lower bacterial load compared with mice fed HFD-S. Further, we found an increased frequency of Ly6G⁺ neutrophils and CD117⁺ hematopoietic stem cells in the bone marrow in mice fed HFD-P at uninfected state. Moreover, neutrophils from mice fed HFD-P have an improved migratory capacity. Since dietary manipulations have an effect on the whole organism, we investigated the transcriptome profile in immunologically and metabolically important organs. Remarkably, the spleen showed a major response to HFD-P, *i.e.*, down regulating both the innate and the adaptive immune system. We further investigated the mechanisms behind the increased frequency of neutrophils in mice fed HFD-P and showed an increased level of the major regulator of granulopoiesis, G-CSF, in the bone marrow. Additionally, there was an increased frequency of neutrophils in organs housing the marginated pool of neutrophils, *i.e.* spleen, liver and bone marrow. Since HFD-P contained different types of PUFAs, both omega-3 and omega-6 PUFAs (ω -3 PUFAs and ω -6 PUFAs), additional investigations aimed to determine which type of fatty acids mediated the beneficial effects. Omega-3 PUFAs were identified as the PUFAs responsible for the positive effects on the immune system and survival in septic infection.

In conclusion, our results show that, beyond their well-recognised anti-inflammatory properties, omega-3 PUFAs have immune-modulating properties, as they influence the transcriptome profile in the spleen, increase the frequency of neutrophils in bone marrow, spleen and liver, as well as, improve neutrophil function, making this type of PUFAs a potential supplementary treatment for sepsis.

Keywords: Immune system, neutrophils, sepsis, polyunsaturated fatty acids, omega-3 fatty acids

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