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Neutrophils *vs.* Pathogenic Fungi

through the magnifying glass of nutritional immunity

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie doktorsexamen framläggs till offentligt försvar i sal E04, byggnad 6E, NUS,
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Abstract
Neutrophils are among the first white blood cells recruited to the site of infection once microbial pathogens enter the host organism. At site, they perform a well-orchestrated chain of processes that aims to kill the microbial invader. Most prominent, neutrophils engulf microbes to inactivate them intracellularly, a process called phagocytosis. Alternatively, neutrophils can release neutrophil extracellular traps (NETs). NETs consist of chromatin decorated with antimicrobial effector proteins – a structure that can entangle bacteria and fungi. Neutrophils are crucial during fungal infections. This is reflected in the increased risk of fungal infections resulting of neutropenia. The concept of nutritional immunity describes every infection as a battle for resources. Those are mostly metal trace elements.
For a long time, neutrophils were seen as powerful, but "mindless", killers with a limited set of actions and no transcriptional capacity, but this view is in the flux.
In the presented thesis, it was my goal to gain new insights into the interplay of neutrophils and fungi – with special attention to metal-nutritional aspects.
We compared human neutrophils lacking the ability to undergo NETosis, due to a non-functional NADPH complex, and neutrophils from the same person that were "cured" by gene therapy. We investigated those NETs and found that their inhibitory activity towards the mold *A. nidulans* depends on calprotectin, a known zinc-chelator.
Considering the high influx of neutrophils, we wanted to unravel the neutrophils' contribution to the metal milieu at the site of infection and trace element changes resulting from NETosis. By combining synchrotron radiation XRF and ICP-MS, we analyzed the neutrophil metallome and the spatial element distribution in activated neutrophils and NETs. Most strikingly, we found neutrophils to be exceptionally high in Fe and the process of NETosis to be reducing available Zn in the surrounding and the early phagosome, possibly by the formation of Zn-rich vesicles.
Using RNA-sequencing, we analyzed the interplay of the *C. albicans* and neutrophils face-to-face. We dissected their transcriptional profile and revealed a manifold response in neutrophils that include cytokine induction and cellular rearrangement. We further were the firsts to explore the transcriptional response of *C. albicans* to NETs. Our data indicates a distinct response compared to intact neutrophils or other known stress triggers. Metal homeostasis was affected in *Candida* in both set-ups.
In summary, this thesis provides new insights into the interaction of fungal pathogens with neutrophils and emphasizes the impact of nutritional aspects on this interplay. A deeper understanding of the nutritional immunity during fungal infection might open up new strategies to tackle fungal infections – a growing threat worldwide.

Keywords
neutrophils, *Candida albicans*, nutritional immunity, metallome, extracellular traps, Zn, Fe

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