7 Summary

Histone modifications in the pathogenesis of bacterial infections

Histone modifications contribute to the regulation of eukaryotic gene transcription. However, the role of chromatin remodelling in immune responses to intracellular pathogens is poorly understood. Focus of this work lied on clarifying the importance of chromatin remodelling mechanisms as well as signaling pathways in response to infections with *Listeria monocytogenes* and *Chlamydophila pneumoniae* as model organism of human endothelial cell infection.

L. monocytogenes and *C. pneumoniae* induced the expression of IL-8 and IFNγ, two cytokines that are of great importance for recruitment of inflammatory cells responsible for bacterial elimination. Furthermore, both bacteria induced the secretion of IL-6, TNFα and G-CSF. By using the HDAC inhibitor Trichostatin A (TSA) *L. monocytogenes*- and *C. pneumoniae*-induced IL-8 secretion was significantly upregulated while treatment with TSA led to an increased pan-acetylation of histone H4 at the *il8* promoter.

Moreover, it was demonstrated that endothelial infection by *L. monocytogenes* and *C. pneumoniae* induced histone modifikations of histone H3 and H4. The main approach of this work was to analyse two specific histone modifications: phosphorylation/acetylation of histone H3 and pan-acetylation of histone H4. It was shown that both pathogens induced time-dependently phosphorylation/acetylation at serin 10/ lysin 14 of histone H3 and pan-acetylation of histone H4, especially at the *il8* promoter. In addition, recruitment of RNA polymerase II and NF-κB/p65 to the *il8* promoter could be detected in a time-dependent manner. Infection with *L. monocytogenes* also demonstrated that the histone acetyl transferase CBP was recruited to the *il8* promoter while HDAC1 disappeared.

Infectionstudies with *L. monocytogenes* showed that histone modifications were p38-MAPK- and ERK1/2-dependent, especially at the *il8* promoter. While recruitment of RNA Pol II, p65 and CBP to the *il8* promoter were shown to be regulated by p38-MAPK and ERK1/2, HDAC1 recruitment depended solely on p38-MAPK. On the other hand, *L. monocytogenes* had no effect on high basal histone acetylation at the *ifnγ* promoter and p38-MAPK and ERK1/2 were not involved in *L. monocytogenes*-induced IFNγ expression.

L. monocytogenes as well as *C. pneumoniae* induced IL-8 production in a Rac1-dependend manner in human endothelial cells. Moreover, both bacteria-induced histone modifications

were Rac1-dependend and recruitment of RNA Pol II and p65 to the *il8* promoter were shown to be reduced after inhibition of Rac1.

Finally, simvastatin, an agent known to have beneficial effects on endothelial function by cholesterol reduction and also known to have blocking effects on Rho proteins, reduced *C. pneumoniae*-induced IL-8 secretion. *C. pneumoniae*-induced histone modifications were impaired after pre-treatment with simvastatin at protein level and specifically at the *il8* promoter. Moreover, recruitment of RNA Polymerase II and NF-κB/p65 to the *il8* promoter was reduced by simvastatin.

Taken together, chromatin remodelling, especially histone modifications, are induced gen-specific after bacterial infection in human endothelial cells. This phenomenon might contribute to the regulation of genexpression.