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Role of SOCS proteins during mycobacterial infections

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ABSTRACT

Mycobacterium tuberculosis is the world's most successful bacterial killer. During infection, mycobacteria reside inside host cells encapsulated within a granuloma structure in the latent, asymptomatic phase of infection. Only 10% of latently infected develop active, infectious tuberculosis months or years after the initial infection. The mechanisms that determine latency and bacterial control as well as protection during active tuberculosis are still not fully understood. Members of the SOCS protein family are regulators of cytokine signaling via inhibition of JAK-STAT activation and their expression is increased during different kinds of infections. Therefore, the purpose of this thesis was to study the role of SOCS1, SOCS2 and SOCS3 during mycobacterial infections.

We demonstrated that infection with *M. tuberculosis in vitro* and in mice strongly upregulated SOCS1 expression. Interestingly, SOCS1 reduced IFN-γ secretion by macrophages in response to IL-12 rather than responses to IFN-γ itself. In line, SOCS1-deficient macrophages showed improved growth control of mycobacteria *in vitro*. Furthermore, in a mouse model of infection, we demonstrated that SOCS1 expression by macrophages impaired bacterial clearance before the onset of protective adaptive immune responses. However, SOCS1 did not hamper adaptive immune-controlled bactericidal mechanisms at later time points. At this stage of infection, SOCS1 expression by non-macrophage cells protected mice from severe immunopathology.

Additionally, we showed that SOCS2 expression was induced in an IRF3-dependent manner after infection with *M. bovis* BCG or incubation with LPS *in vitro*. However, SOCS2-deficient and control mice infected with *M. tuberculosis* displayed similar bacterial burdens in the lungs.

In studying the role of SOCS3 in different mouse models, we found that the lack of SOCS3 in either myeloid or T cells dramatically increased susceptibility to *M. tuberculosis* infection. During infection, SOCS3 expression in macrophages and dendritic cells was required to prevent an inhibitory effect of IL-6 on TNF and IL-12 secretion and elevated IFN-γ expression by CD4+ T cells. More detailed studies revealed that the lack of SOCS3 in myeloid cells could be mimicked by mutating the SOCS3 binding site of the gp130 receptor. This indicates that among the receptors, which can be regulated by SOCS3, the control over the IL-6 family gp130 receptor is fundamental for proper immune responses. Surprisingly, mice bearing SOCS3-deficient T cells were not susceptible to BCG infection. Moreover, a proper defense against challenge with *M. tuberculosis* infection was restored if mice deficient for SOCS3 in T cells had been BCG-vaccinated.

In conclusion, we demonstrated a pivotal role of SOCS1 and SOCS3 on the outcome of infection with *M. tuberculosis*. SOCS1 expression allows fast bacterial growth during the early phase of infection and protects from severe inflammation during later stages. SOCS3 expression in myeloid and T cells independently mediates resistance to *M. tuberculosis* infection by modulating T cell functions. Based on the obtained data, we suggest that SOCS3-regulated pathways are promising targets for future therapies as well as vaccination strategies.

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