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SOCS-3 in macrophages/neutrophils mediates protection against *Mycobaterium tuberculosis* infection

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Ineffective macrophage effector mechanisms contribute to persistence of *Mycobacterium tuberculosis* (*Mtb*) infection and may also counteract an efficiently protective immunity after immunisation against tuberculosis. Suppressor of cytokine signalling (SOCS) 3 is a feedback inhibitor of various signalling pathways in macrophages. To assess the putative inhibitory capacity of SOCS3 on macrophage activation during infection with *Mtb*, macrophage/neutrophil-specific SOCS3 deficient ($LysM^{cre}SOCS3^{lox/lox}$) mice were utilised. *In vitro*, $LysM^{cre}SOCS3^{lox/lox}$ macrophages exhibited an unaltered inflammatory cytokine production upon cytokine stimulation and after infection with low doses of *Mtb*. In contrast, infection with higher doses led to a loss of antimycobacterial effector functions. Accordingly, aerosol infection of $LysM^{cre}SOCS\text{-}3^{lox/lox}$ mice resulted in an utterly immunocompromised phenotype with remarkably high bacterial loads, necrotising pulmonary granulomas and premature death. Detailed analysis revealed that the increased susceptibility to *Mtb* infection was accompanied by a hyperinflammatory immune response as well as an enhanced development of alternatively activated macrophages. This alternative activation of macrophages leads to an increased expression of arginase-1, thereby providing a niche for mycobacteria to grow. Our data indicate a new, pivotal role of SOCS3 for macrophage activation, enabling efficient killing of intracellular mycobacteria in classically activated macrophages.

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