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Influenza A virus-induced IL-6 storm is regulated by SOCS3

Ji-Long Chen[1, 2], Ruoxiang Yan[1], Jing Ouyang[2], Biao Chen[2] and **Xiancheng Zeng[1]**
[1]Fujian Agriculture and Forestry University, China
[2]Chinese Academy of Sciences, Beijing, China

Influenza A virus (IAV) is still a major public health threat in the world, as indicated by enormous severe pneumonia resulted from the virus infection every year. IL-6-involved excessive inflammatory response to IAV infection profoundly contributes to IAV pathogenesis. However, precise regulatory mechanisms underlying such a response are poorly understood. Here we found from both *in vivo* and *in vitro* studies that IAV not only induced surge of IL-6 release, but also greatly upregulated expression of SOCS3, the potent suppressor of IL-6/STAT3 signaling. Interestingly, there existed a cytokine-independent mechanism of the robust induction of SOCS3 by IAV at least at early stage of the infection. Furthermore, we generated SOCS3-knockdown transgenic mice (TG), and surprisingly observed from virus challenge experiments using the TG mice that disruption of SOCS3 expression provided significant protection against IAV infection, as evidenced by attenuated acute lung injury, a higher survival rate of infected animals and lower viral load in infected tissues as compared with those of wild-type littermates under same challenge. The activity of NFκB and the expression of its target gene IL-6 were remarkably suppressed in SOCS3-knockdown A549 cells and TG mice after infection with IAV. Moreover, we defined that enhanced STAT3 activity caused by SOCS3 silencing was important for the negative regulation of NFκB and IL-6. These findings establish a critical role for IL-6-STAT3-SOCS3 axis in the pathogenesis of IAV, and suggest that influenza virus has evolved a strategy to circumvent IL-6/STAT3-mediated immune response through upregulating SOCS3.

chenjl@im.ac.cn