Novel insights in molecular mechanisms of pathogen-host interactions during influenza virus and *Staphylococcus aureus* co-infection

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Influenza viruses (IV) are the causative agents for severe respiratory diseases resulting in significant morbidity and mortality worldwide. Major complications upon influenza are due to secondary bacterial infection, often leading to severe pneumonia. Typical bacterial species isolated from patients with secondary infections are common colonizers of the nasopharynx, such as *Staphylococcus aureus* (*S. aureus*). Given the enormous socio-economic burden caused by IV and *S. aureus* super-infection, it is mandatory to unravel the underlying disease mechanisms. Descriptive data from clinical studies and animal models have improved our understanding of how co-pathogenesis between IV and bacteria might occur. One hallmark of severe infection is the dysregulation in immune responses accompanied by increased cytokine and chemokine expression resulting in detrimental inflammation, enhanced pathogen load and tissue damage. Additionally, it is well established that pathogen replication and host cytokine responses are controlled by pathogen-regulated signaling events. Nonetheless, the complex interplay of pathogen-pathogen and pathogen-host interactions that affect cellular regulatory mechanisms is only in part understood.

Thus, we established IV and *S. aureus* co-infection model systems that allow the investigation of cellular signal transduction processes in human lung epithelial cell-lines. By use of these model systems, we could verify enhanced cytokine and chemokine expression, higher pathogen load as well as increased cell damage upon IV and *S. aureus* co-infection in vitro. Detailed molecular analysis indicated that *S. aureus* inhibits IV-induced type I interferon response on the level of STAT-1 phosphorylation resulting in less STAT-1 and STAT-2 dimerization and reduced activation of interferon stimulated genes. In consequence the first line of defense against IV infection is blocked and viral replication is boosted. Further investigation of cell-death mechanisms revealed detrimental cell damage in super-infection scenarios. However, our data surprisingly show that, despite enhanced cell damage in presence of both pathogens, *S. aureus* did not increase but rather inhibit IV-induced apoptosis. We provide evidence for a *S. aureus*-mediated switch from apoptosis to necrotic cell death of IV-infected cells promoting bacterial survival and spread.

In conclusion, we already identified different mechanisms of *S. aureus*-mediated interference with IV-induced signal transduction processes that might contribute to co-virulence.