Elucidation of mechanism underlying exacerbation of bacterial pneumonia following influenza infection for development of preventive and therapeutic measures against superinfection

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Abstract

Influenza A virus (IAV) infection predisposes the host to secondary bacterial pneumonia, known as a major cause of morbidity and mortality during influenza epidemics. Although it is generally accepted that preceding IAV infection leads to increased susceptibility to secondary bacterial infection, details regarding the pathogenic mechanism during the early stage of superinfection remain elusive. Here, we focused on the interaction of IAV-infected cells and *Streptococcus pneumoniae*, which revealed that human epithelial cells infected with IAV exhibit a cell-surface display of GP96, an endoplasmic reticulum chaperon. Notably, extracellular GP96 was shown to impart efficient adherence for secondary infection by *S. pneumoniae* and GP96 inhibition ameliorated lung pathology of superinfected mice, indicating it to be a useful target for development of therapeutic strategies for patients with superinfection.

Background & Results

Secondary bacterial infections following a primary influenza virus infection are frequent complications, and result in the majority of related deaths during seasonal and pandemic influenza outbreaks. *S. pneumoniae* is the most commonly identified pathogen in secondary bacterial pneumonia cases. Although antibiotics remain the mainstay of therapy for affected patients, the increasing prevalence of multidrug-resistant *S. pneumoniae* is a serious public health concern worldwide. Thus, development of host-directed therapeutics is receiving focus as an alternative approach to treating secondary bacterial pneumonia following influenza. Analysis of interactions between IAV-infected human epithelial cells and *Streptococcus pneumoniae* revealed that infected cells ectopically exhibited the endoplasmic reticulum chaperon GP96 on the surface. Importantly, efficient pneumococcal adherence to epithelial cells was imparted by interactions with extracellular GP96 and integrin α_V, with the surface expression mediated by GP96 chaperone activity (Fig. 1). Furthermore, abrogation of adherence was gained by chemical inhibition or genetic knockout of GP96. Direct binding of extracellular GP96 and pneumococci was shown to be mediated by pneumococcal oligopeptide permease components. Additionally, IAV infection induced activation of calpains and Snail1, which are responsible for degradation and transcriptional repression of junctional proteins in the host, respectively, indicating increased bacterial translocation across the epithelial barrier. Notably, treatment of IAV-infected mice with the GP96 inhibitor enhanced pneumococcal clearance from lung tissues and ameliorated lung pathology (Fig. 2).

Significance of the research and Future perspective

Our data indicate that GP96 functions as a multifunctional exacerbation factor to promote pneumococcal colonization, dysfunction of lung tissue barrier, and probably dysregulation of immune responses as well, during secondary bacterial pneumonia following an influenza infection. Because of the complexity of the pathogenesis, a balanced combination of antimicrobial agents and immunomodulators could be more effective for prospective therapeutics. We believe that GP96 is a potential target for development of promising therapeutic strategies, including combination therapies as alternatives to conventional antibiotics and antiviral agents administered for broad-spectrum prevention, as well as management of secondary bacterial infections following influenza.

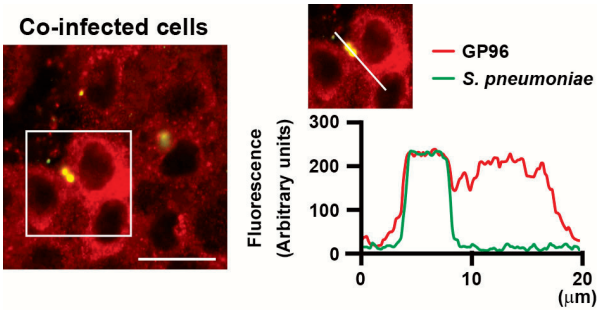

Fig. 1. IAV infection-induced surface display of GP96 promotes pneumococcal adherence to human alveolar epithelial cells.

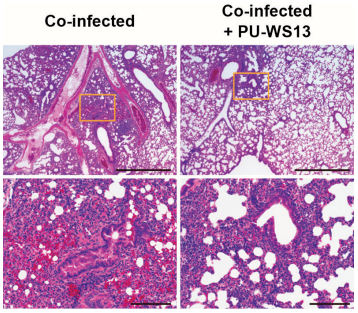

Fig. 2. Lung tissues obtained mice were subjected to HE staining. Boxed area is magnified and shown in lower panels. PU-WS13, GP96 inhibitor.

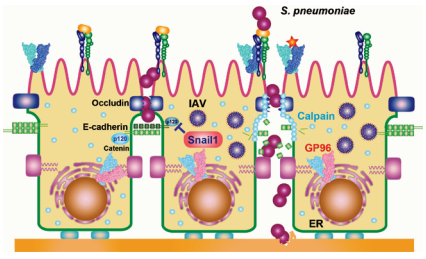

Fig. 3. Mechanisms underlying exacerbation of bacterial pneumonia following influenza infection.

Patent

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