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EDITORIAL



# Mucin 1 is a novel glycoprotein involved in host defense against invasive pneumococcal disease

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*Streptococcus pneumoniae* (also termed pneumococcus) is one of the major human pathogens that affect particularly to children and elderly people, being responsible for high rates of morbidity and mortality worldwide.[1,2] This bacterium colonizes asymptomatically the human nasopharynx in a process known as carrier state, causing acute otitis media, sinusitis, community-acquired pneumonia and serious diseases such as bacteremic pneumonia, sepsis and meningitis.[2,3] Resolution of the infectious process depends on the ability of the microorganism to cause invasive disease and the efficient recognition and clearance of the invading pathogen by the host immune response.[3,4] In this scenario, professional phagocytes and host epithelial cells play an important role in inflammatory and immune responses against the infection as bacterial eradication largely depends on the efficiency of different receptors expressed on host cells to recognize, internalize and kill the pathogen.[5-9] Epithelial mucins are a heterogenous family of large complex glycoproteins that can be divided into 3 different subfamilies in which cell-surface mucins contains many of them.[10] One of these receptors involved in host defense, is Mucin 1 (MUC1) that is a cell membrane-associated glycoprotein expressed on the majority of epithelial cells including the respiratory tract and the middle ear, which are target sites for pneumococcal infection, and also in immune cells such as B cells, T cells, macrophages and dendritic cells.[11,12]

In this issue of Virulence, Dhar and colleagues demonstrate the protective role of MUC1 against invasive pneumococcal disease.[13] Using wild-type and *Muc1*$^{-/-}$ mice, the authors investigated the impact of MUC1 deficiency in pneumococcal pathogenesis. In terms of nasopharyngeal carriage, similar levels of colonization were found in both groups of mice demonstrating that MUC1 is not involved in the carrier state. However, in a pneumonia model of infection, lack of MUC1 was associated to high levels of *S. pneumoniae* in the lungs, contributing to bacterial dissemination from the respiratory tract to the systemic circulation, causing invasive disease.[13] This is of great relevance from the respiratory perspective as pneumonia is the leading killer of children worldwide causing more deaths than AIDS, malaria and measles combined,[14] being *S. pneumoniae* the major etiologic agent of community acquired pneumonia in the pediatric and adult populations.

Furthermore, the authors confirm a novel role for MUC1 in host immune defense against this pathogen. In this sense, bacterial killing was impaired in macrophages from *Muc1*$^{-/-}$ mice, confirming, that MUC1 promotes the phagocytosis of *S. pneumoniae*.[13] The lung contains alveolar macrophages which are both sentinels and the first line of defense against infection and, bacterial clearance from lungs and blood, depends on the efficiency of \host phagocytes to recognize and destroy the pathogen.[15] In the case of Gram-negative microorganisms such as *Pseudomonas aeruginosa* and *Escherichia coli*, inhibition of MUC1 expression enhances the phagocytic activity of human macrophages and the explanation for this phenotype is because MUC1 may attenuate bacterial adhesion to macrophages.[12] One possible reason for this discrepancy might be due to the presence of LPS in Gram-negative bacteria although further research is needed to address this possibility.

Overall, the findings by Dhar and colleagues demonstrate for the first time the protective role of MUC1 against *S. pneumoniae*. In this study, the authors observed that *Muc1*$^{-/-}$ mice, despite having greater

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numbers of monocytes and macrophages in the lung, had an impaired ability to clear the bacteria, confirming the importance of MUC1 in the recognition and killing of *S. pneumoniae* in the respiratory tract and the systemic circulation.[13] Although the expression of MUC1 in the lung is relatively low during the early stage of bacterial infection,[16] the levels of MUC1 are triggered by the pro-inflammatory cytokine TNF-$\alpha$ to regulate inflammation.[16,17] This is important because MUC1 has been shown to play a critical role in host defense, reducing the inflammatory response after infection of the respiratory tract by syncytial virus or non-typeable *Haemophilus influenzae*.[18,19] These results are consistent with the protective role of MUC1 against *S. pneumoniae*, as *Muc1*$^{-/-}$ mice had significantly increased levels of pro-inflammatory cytokines in the lung compared with wild-type mice, confirming that MUC1 ameliorates the inflammatory response of the airway induced by pneumococcal infection.[13]

Since mucin glycoproteins are one of the major constituents of epithelial cells lining the gastrointestinal tract with many cells expressing multiple members of this family, their protective role neutralizing the invading pathogen is critical to prevent the infection of this mucosal barrier by enteric pathogens.[11,20] In this sense, MUC1 protects against bacterial infection by *Helycobacter pylori* and *Campylobacter jejuni*.[21,22] The fact that MUC1 plays critical roles in protection against a diverse variety of important human bacterial pathogens affecting different locations of the host including the respiratory tract and the gastrointestinal barrier, demonstrate the importance of this molecule in host defense. Further research in this field is necessary as it could lead to the development of novel strategies to prevent or reduce the impact of infectious diseases affecting host sites that are continuously exposed to microbial intruders such as the airway and the gastrointestinal tract. Future studies exploring the interaction of mucin glycoproteins with relevant pathogens should be considered as a priority, as mucins are important components of host cells with critical roles in innate and adaptive immune responses.

## Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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