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Role of epithelial mucins during airway infection

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Abstract

Airway surface fluid contains two layers of mucins consisting mainly of 5 different mucin gene products. While the outer layer contains two gel-forming mucins (MUC5AC and MUC5B) that are tightly associated with various biologically active, defensive molecules, the inner layer contains three membrane-tethered mucins (MUC1, MUC4 and MUC16) shed from the apical cell surface. During airway infection, all of these mucins serve as a major protective barrier against pathogens. MUC1 mucin produced by virtually all the surface columnar epithelial cells in the respiratory tract as well as Type II pneumocytes in the alveoli plays an additional, perhaps more critical role during respiratory infection by controlling the resolution of inflammation that is essential to prevent the development of inflammatory lung disease.

Keywords

MUC1 mucin; *Pseudomonas*; Toll-like receptor; airway infection; inflammation and anti-inflammation

1. Introduction

Airway lining fluid, or mucus, serves as the first line of defense during airway infection. Pathogens trapped in the mucus layer are first removed by the mucociliary clearance mechanism of the underlying airway epithelium as well as macrophages and then by neutrophils recruited into the airways in response to inflammatory mediators released by epithelial cells and macrophages. Mucins are produced by goblet cells of surface epithelium and mucous cells of submucosal glands. The quality and quantity of mucins determine the viscoelastic property of mucus which is critical for the mucociliary clearance. Recent progress in airway mucin research has revealed that the roles of mucins during airway infection are more than just mucociliary clearance. This review will focus on the "unconventional" roles of mucins during airway infection. For the readers who may not be familiar with mucins, I will start with some basic structural information of mucins that should be useful in understanding their functional roles during airway infection. By convention, MUC represents human mucin and Muc for animal mucin. However, these abbreviations will be used somewhat interchangeably in this review just for the purpose of convenience.

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2. Structure of mucins

Mucins are high molecular weight glycoproteins with variable numbers of tandem repeats of certain numbers of amino acids that are usually rich in serine, threonine and proline. Both serine and threonine are the sites of glycosylation of the peptide backbone through O-glysosidic linkage with N- acetylgalactosamine of the oligosaccharides, thus called O-linked glycoproteins. More detailed structural information of mucins is summarized in a number of reviews [1–4]. At least 22 mucin genes have been cloned in human [4–7], of which 16 have been identified in the lung (MUC1, MUC2, MUC4, MUC5AC, MUC5B, MUC7, MUC8, MUC11, MUC13, MUC15, MUC16, MUC18, MUC19, MUC20, MUC21, and MUC22) [4,6,6–9]. Deduced amino acid sequences of the cloned mucin genes revealed that there are two types of mucins – secreted mucins and membrane-tethered mucins. Seven mucin gene products (i.e., MUC2, 5AC, 5B, 6, 7, 8 and 19) are characterized as secreted and the remaining 10 mucin gene products are membrane-tethered [3,7]. Most of the transmembrane mucins are expressed on the apical surface of lining mucosal epithelial cells that are in contact with the outside environment. This suggests a defensive role of mucins for the host.

3. Mucins as a scaffold protein

Based on its anatomical location in the body as well as the complex structure of mucins, it was suggested quite some time ago that mucus has multifaceted properties necessary for host defense: anti-microbial, anti-protease, and anti-oxidant activities [10]. Jacquot et al [10] first reported the presence of these properties in airway secretions. Kim et al [11,12] demonstrated that airway mucins are extremely hydrophobic and guanidine hydrochloride (4–6 M), one of the most chaotrophic agents, could not completely dissociate mucins from other macromolecules present in airway secretion. It was postulated that the hydrophobic property may allow for effici[1]ent packaging of secreted mucins (>10^6 Dalton) with highly thermodynamic nature into the distinct secretory granules [13]. Recent proteomics analysis of mucins revealed that mucins are tightly associated with various proteins [14,15], including those with anti-microbial, anti-protease, anti-oxidant, or anti-inflammatory properties [15]. Thus, mucins are like a large aircraft carrier carrying a variety of “weapons” to be used against the invading pathogens. It may be possible that association of mucins with the bioactive molecules are formed inside the secretory granules before but not after exocytosis as previously suggested [16], such that they can interact with invading pathogens more effectively and efficiently upon exocytosis. How and when such association takes place in the goblet cell and is packaged into a mucous granule remains to be uncovered.

4. Roles of mucins during airway infection

Although 16 out of 22 mucin genes have been identified in the lung, their functions are largely unknown. A recent review by Sheehan et al [17] describes the roles of five major mucns (MUC5AC, MUC5B, MUC1, MUC4, and MUC16) in protecting and stabilizing the ciliated surface and building the gel in the airway epithelium. Although focused exclusively on intestinal mucins, a recent review by McGuckin et al [18] on the interaction of mucins with intestinal pathogens will greatly help us better understand the role of mucins during respiratory infection. In this review, I will focus mainly on the role of MUC1 mucin during airway infection.

4.1. MUC1 mucin

4.1.1. MUC1 mucin is expressed by lung epithelial cells—MUC1 was the first mucin gene to be cloned [19,20] as a cancer antigen. It is a membrane-tethered mucin that is located on the apical surface of mucosal epithelial cells as well as hematopoietic cells [21]. Although the expression of MUC1 in lymphocytes as well as dendritic cells is well

established, its expression in other hematopoietic cells seems less clearly defined. Its expression has also been reported in corneal endothelial cells [22]. Whether other endothelial cells also express MUC1 is totally unknown. Details of the structure of MUC1 as well as its roles in cancer have been reviewed previously [1,23]. The presence of mucin-like glycoproteins on the surface of airway epithelial cells as those releasable by neutrophil elastase was documented in the hamster by Kim et al [24]. Expression of MUC1/Muc1 in the lung tissues as well as airway epithelial cells was later reported by Pemberton et al [25] and Hollingsworth et al [26], respectively. Using a cDNA library developed from primary hamster tracheal epithelial cells, Park et al [27] identified the expression of the *Muc1* gene. Using the same cells, Paul et al [28] identified the presence of Muc1 protein in the plasma membrane fraction. Its expression in alveolar type II cells has also been documented [29]. Thus, it seems that MUC1/Muc1 is expressed on the apical surface of the lining epithelial cells of the lung.

4.1.2. MUC1 is a receptor for *Pseudomonas aeruginosa*—What is the role of this cancer antigen in the normal lung? Lillehoj et al [30,31] first demonstrated that hamster Muc1 expressed on the surface of CHO cells is an adhesion site of *Pseudomonas aeruginosa* (Pa), binding of which to the extracellular domain of Muc1 in CHO cells results in tyrosine phosphorylation on the cytoplasmic domain (CT) of MUC1 and the subsequent activation of ERK2 [32]. Tyrosine phosphorylation of MUC1 CT was also demonstrated in a chimera protein [33] in which MUC1 CT is covalently linked to the extracellular and plasma membrane domains of CD8 when cells expressing the chimera were treated with anti-CD8 antibody [33,34]. Using the chimera system, Wang et al [35] identified 4 tyrosine moieties on the MUC1 CT that are phosphorylated upon activation with anti-CD8 antibody as Y20, Y35, Y46, and Y60 which constitute consensus sequences for binding of PI3K, Shc, EGFR or Src, and Grb2, respectively [36]. Recently, the specific binding of Pa to the extracellular domain of MUC1 was also confirmed in human lung epithelial cells [37]. Given the importance of airway epithelial cells as a defensive barrier during Pa infection, it was originally speculated that MUC1/Muc1 may play an important role in facilitating Pa clearance during infection.

4.1.3. MUC1 plays an anti-inflammatory role during airway infection—To understand the potential role of Muc1 during airway Pa infection, $Muc1^{-/-}$ mice and their wild type littermates ($Muc1^{+/+}$) were infected with Pa and the degree of lung inflammation was compared at 4 hours following Pa infection. $Muc1^{-/-}$ mice showed increased KC (mouse ortholog of human IL-8) and TNF-α levels as well as increased numbers of neutrophils in BALF and increased clearance of Pa compared with $Muc1^{+/+}$ mice indicating that the absence of Muc1 facilitates airway inflammation [38]. Thus, these results suggested that MUC1 plays an anti-inflammatory role during airway Pa infection contrary to the initial prediction. The anti-inflammatory role of Muc1 during airway Pa infection was confirmed [39].

4.1.4. The anti-inflammatory effect of MUC1 is mediated through inhibition of TLR signaling—The study with Pa infection in $Muc1^{-/-}$ mice suggested the inhibitory effect of MUC1 on Pa-induced inflammation [38]. Since Pa-induced inflammation is induced mainly by activation of Toll-like receptor (TLR)5 by its flagellin [40]and because both TLR5 and MUC1 are present on the apical surface of airway epithelial cells, it was postulated that the presence of MUC1 may suppress TLR5 signaling. The inhibitory effect of MUC1 on TLR5 signaling was clearly demonstrated in cultured epithelial cells [41]. In addition, more interestingly, it has been shown, using various cultured cells, that the anti-inflammatory effect of MUC1 is not limited to TLR5 but all the other TLR signaling including TLR2, 3, 4, 7, and 9 [42] suggesting that MUC1 may be an universal negative

regulator of TLR signaling. Furthermore, the anti-inflammatory effect of MUC1 did not require the whole molecule but only the cytoplasmic domain of MUC1 [38,42]. Given the importance of inflammation during the early stage of Pa infection and the "universal" anti-inflammatory effect of MUC1, a major speculation has been generated that the expression of Muc1 in the lung might be harmful to the host. This critical question prompted us to investigate the regulation of Muc1 expression in the airways.

4.1.5. MUC1 is upregulated during inflammation by TNF-α and plays a key role in the resolution of inflammation—Since MUC1 is cleaved by neutrophil elastase (NE) produced during inflammation, it was hypothesized that NE can upregulate MUC1. Using A549 cells, Kuwahara et al demonstrated that NE can upregulate MUC1 through a signaling pathway involving PKCδ → Dual Oxidase 1 → Reactive oxygen species → TNF-α converting enzyme → TNF-α → TNFR1 → ERK2 → Sp1 [43–45]. It was interesting that TNF-α, a major proinflammatory mediator during airway infection, has the ability to upregulate MUC1 and is required for NE-induced MUC1 upregulation. To assess the contribution of TNF-α to MUC1 levels during airway infection, animals ($Muc1^{+/+}$, $Muc1^{-/-}$, and $TNFR^{-/-}$) were treated with Pa and both TNF-α and MUC1 levels were monitored over time. The results showed that Muc1 levels of uninfected lungs of $Muc1^{+/+}$ mice were relatively low and increased steadily following Pa infection reaching a peak at 2–4 days. However. $TNFR^{-/-}$ mice failed to upregulate Muc1 following Pa infection and the inflammatory responses of $TNFR^{-/-}$ mice were very close (only slightly lower) than those of $Muc1^{-/-}$ mice [39]. Both $Muc1^{-/-}$ and $TNFR^{-/-}$ mice failed to resolve Pa-induced inflammation. These results not only supported the previous notion that TNF-α upregulates MUC1 but also indicated that TNF-α production is required for Pa-induced Muc1 upregulation. In addition, the results of this study helped us to answer the critical question as to whether the anti- inflammatory activity of MUC1 is beneficial or harmful during bacterial infection. Thus, the anti-inflammatory role of MUC1 comes into play at the late stage of infection mainly as a result of the increased levels of TNF-α produced at the early stage of infection. This concept is summarized in Fig. 1. The existence of such a feedback loop of inflammation involving TNF-α (pro-inflammatory) and MUC1 (anti-inflammatory) has also been further supported in A549 cells treated with respiratory syncytial virus [46] or nontypeable *Hemophilus influenzae* [47]. In summary, airway infection results in the production of proinflammatory mediators including TNF-α through activation of appropriate TLRs, which in turn upregulate MUC1 that suppresses TLR signaling, which results in cessation of the production of proinflammatory mediators and ongoing inflammation.

4.1.6. Mechanism of crosstalk between MUC1 and TLRs—An important question that still remains largely unknown is how the increased levels of MUC1 can suppress TLR signaling during airway infection/inflammation. This study is currently under way in our laboratory. However, our preliminary data (unpublished) with Pa-induced TLR5 signaling suggest that the site of inhibition of TLR5 signaling by MUC1 is at the level of MyD88 recruitment. Briefly, MUC1 binds to TLR5 at its TIR domain thus preventing the recruitment of MyD88 during TLR5 activation by Pa or flagellin. Whether MUC1 phosphorylation is required for the inhibitory effect and, if so, which kinase(s) is responsible for phosphorylation are currently under investigation in our laboratory.

4.1.7. Shedding of MUC1—It has been shown that MUC1, a membrane-tethered glycoprotein, is shed by proteolytic cleavage, both spontaneously and by various stimuli including TNF-α and PMA [48]. Among the proteases responsible for MUC1 shedding are neutrophil elastase [24,43,49], TACE [48], MT1 MMP [50], MMP-14 [51], and gamma-secretase [52]. The functional significance of MUC1 shedding is not fully understood. Given

the ability of the MUC1 ectodomain to bind the invading bacteria [30,37,51], it has been postulated that shed MUC1 may serve as a decoy receptor [51] to minimize the direct interaction with the epithelial cell surface and subsequent cell injury. It might also be possible that shed MUC1 may serve as an opsonin to facilitate bacterial clearance during infection.

4.2. Other membrane-tethered mucins (MUC4 and MUC16)

In addition to MUC1, both MUC4 and MUC16 have been shown to be produced and released by airway surface epithelial cells [14]. Sheehan et al [17] demonstrated that shed mucins form a gel in the immediate vicinity of the apical cell surface, likely serving as a protective barrier against invading pathogens and chemicals. How and when these membrane glycoproteins are cleaved remains largely unknown and will be important questions to address in the context with airway infection and inflammation.

4.3. Gel-forming mucins (MUC2, MUC5AC, MUC5B and MUC19)

These are four major gel-forming mucins found in the lung. MUC2 is the major intestinal mucin and Muc2 knockout mice develop colorectal cancer [53]. MUC2 has also been shown to be expressed in the lung [54]. It has been reported that the MUC2 gene is upregulated by *Pa* LPS in both surface epithelium and submucosal glands of human bronchial explants [55] as well as by both Gram(+) and Gram(−) bacteria in both bronchial explants and cultured epithelial cells [56]. On the other hand, An et al [57] reported that MUC2 gene is downregulated by retinoic acid in primary tracheobronchial epithelial cells of human and nonhuman primates. However, Hovenberg et al [58] as well as Thornton [59] demonstrated that the MUC2 was not detectable in both normal and pathologic human sputum samples based on an immunoassay, suggesting that MUC2 is not a major mucin produced in the lung. A recent proteomics analysis of both cultured epithelial cell secretions and patients' sputum samples supports this notion [14]. However, the function of MUC2 in the lung remains still uncertain.

MUC5AC and MUC5B are the major gel-forming mucins in the airway and thus believed to contribute to both the defensive barrier function and the rheology of airway mucus. For details of their biochemistry, see a recent review by Thornton [3]. MUC5AC has been shown to be the goblet cell mucin [60] whereas MUC5B the submucosal gland mucin [61]. MUC5AC has been widely used as a marker for goblet cell metaplasia [62]. Recent studies, however, have demonstrated that MUC5B is the major type of mucin produced by goblet cells [14]. Although the exact roles of MUC5AC and MUC5B in the airways remain to be fully elucidated, it has been suggested that MUC5AC expression is inducible during airway inflammation [63], whereas MUC5B expression is constitutive [63,64]. It has also been shown that MUC5AC is more associated with asthma [63,65,66], whereas MUC5B with COPD [67]. Airway disease associated with mucus dysfunction has been recently reviewed [68]. Recently, a MUC5B promoter polymorphism has been associated with pulmonary fibrosis [69]. It is expected that their roles during airway infection will be uncovered very soon with the current availability of their knockout mice.

MUC19, the major salivary glandular mucin [70], has also been identified in tracheolarynx [71]. However, its role in the lung remains unknown.

Although these gel-forming mucins are present mainly in the interciliary space outside the layer of microvilli where membrane-tethered mucins are present [23], the fact that all these mucins form a major protective barrier against the invading pathogens or chemicals seems to suggest the presence of possible interactions between and among these mucins. In fact, mice with a defective CFTR or CF mice have mucus accumulation in the small intestine,

however, making these mice Muc1 deficient (CF/Muc1$^{-/-}$ mice) prevented mucus accumulation [72]. Interestingly, the types of intestinal mucins affected by Muc1 were not limited to Muc1 suggesting the modulatory effect of Muc1 on other mucins in this animal model [73]. Interactions among various airway mucins, both structurally and functionally, during physiological and pathological conditions are totally unknown and need active research.

5. Conclusion

Airway surface fluid contains two layers of mucins consisting mainly of 5 different mucin gene products. While the outer layer contains two gel-forming mucins (MUC5AC and MUC5B) that are tightly associated with various biologically active, defensive molecules, the inner layer contains three membrane-tethered mucins (MUC1, MUC4 and MUC16) shed from the apical cell surface. During airway infection, all of these mucins serve as a major protective barrier against pathogens. MUC1 mucin produced by virtually all the surface columnar epithelial cells in the respiratory tract as well as Type II pneumocytes in the alveoli plays an additional, perhaps more critical role during respiratory infection by controlling the resolution of inflammation to prevent the development of inflammatory lung disease.

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Abbreviations

CT	cytoplasmic tail
NE	neutrophil elastase
PA	*Pseudomonas aeruginosa*
TLR	Toll-like receptor

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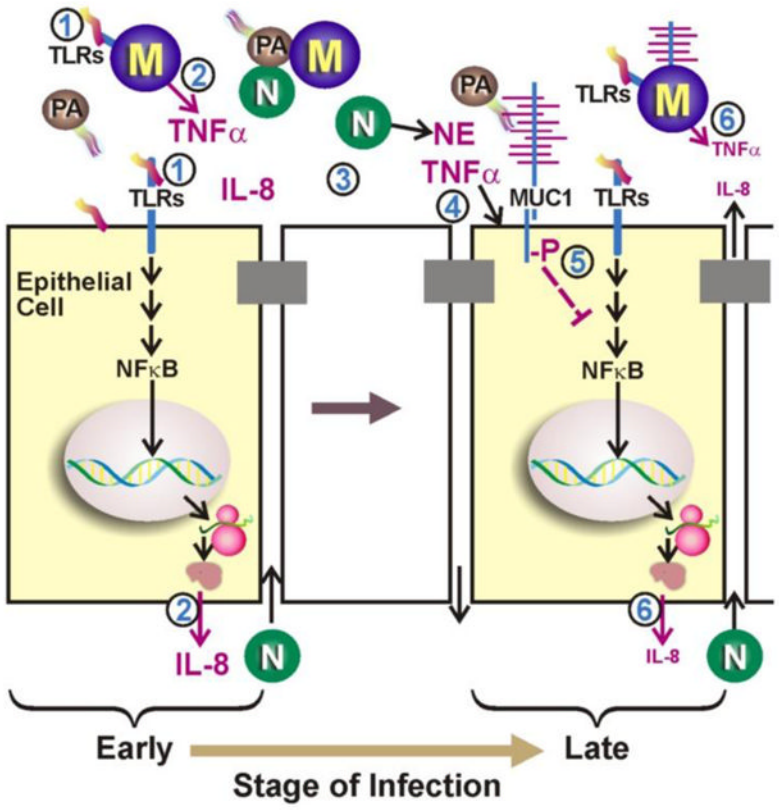

Fig. 1. Anti-inflammatory role of MUC1 during airway infection

(Step 1) During the early stage of infection by *P. aeruginosa* (PA), bacterial PAMPs (e.g. flagellin) activate TLRs and NF-κB on epithelial cells and macrophages (M). (2) Activation of NF-κB leads to increased expression of TNF-α and of IL-8, which are subsequently secreted. (3) IL-8 recruits neutrophils (N) across the epithelial barrier that release NE into the lumen of the airways. (4) NE and TNF-α up-regulate *MUC1* gene expression resulting in increased expression of MUC1 mucin at the apical surface of lung epithelial cells. (5) During the late stage of infection, tyrosine phosphorylation of MUC1 CT domain leads to inhibition of TLR signaling and (6) down-regulation of inflammation. (Fom Kim and Lillejoj [36])