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The complement system in the airway epithelium: An overlooked host defense mechanism and therapeutic target?

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Keywords

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The airway epithelium, from the nasal cavity to the alveoli, persistently encounters toxins and pathogens. If the invader clears the mucus and breaches the epithelium, it must be contained by an innate immune system while awaiting arrival of the adaptive immune system. Hence, we need a biological process to immediately recognize, engage, and destroy a pathogen. The complement cascade is the prototype of such an innate process. It quickly amplifies based on cleavage of its most abundant complement protein: C3 to C3a and C3b (Fig 1, *A*). C3a is a vasodilator and chemoattractant for neutrophils and monocytes, whereas C3b is an opsonin for pathogens and debris. This cleavage (and thus, activation) is triggered primarily in 3 ways: antibody binding to antigen (classical pathway), mannose-binding lectin attaching to oligosaccharides/sugars (lectin pathway), or engagement of a feedback loop to deposit C3b onto a target (alternative pathway).[1]

Complement activation is viewed traditionally as occurring in the blood because of abundant hepatic production and secretion of most of its components. However, multiple cell types are also known to synthesize complement proteins.[1] Those synthesized by resident and invading immune cells have been summarized recently.[2] In contrast, less is known about production and activation of complement in local tissues in contact with the environment, such as the airway. Moreover, whether local complement activation worsens or mitigates injury has been inadequately investigated in most organ systems. In this minireview, we appraise the literature published in the last 3 years on locally synthesized complement proteins in the airway and their potential role in patients with respiratory disease.

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ALLERGIC RHINITIS AND ASTHMA

Unbiased transcriptomic approaches have provided insight into complement expression after environmental exposures. Patients with allergic rhinitis who underwent nasal allergen challenge with grass pollen demonstrated upregulated transcripts of the complement protein properdin *(CFP)* and C5a receptor *(C5aR1)* in their nasal mucosal specimens, along with the IL-1 family of cytokines (IL-1α and IL-1β), T_H2 cytokines (IL-4, IL-5, and IL-13), and interferons.[3] Prednisone downregulated *CFP* and *C5aR1* in some but failed in 7 of 19 subjects, which highlights variation in the immune response from patient to patient in those with allergic rhinitis and asthma. These patients also had variable baseline *IL33* mRNA levels. Thus, the underlying genetic predisposition, as well as baseline levels of cytokines, influenced complement gene expression and accounted for why patients had a variable response to prednisone.

Expression of properdin, a positive regulator of the alternative pathway (Fig 1, *A*), is increased in the bronchoalveolar lavage (BAL) fluid of asthmatic patients. The pathophysiologic correlation in a mouse model has been described elsewhere.[E44] C5aR1 binds C5a, with the latter generated by means of cleavage of C5 downstream of C3 activation (Fig 1, *A*). Although there are no clinical trials yet targeting C5aR in asthmatic patients, preclinical studies showed that C5aR1 antagonism decreased BAL fluid and parenchymal inflammatory cells, IL-13 levels, and T_H2 cytokine gene expression without reducing serum IgE levels in OVA- sensitized and challenged mice.[4] Hence, properdin and C5aR1 should be evaluated further as potential therapeutic targets for difficult-to-treat allergic rhinitis and asthma.

CYSTIC FIBROSIS

Complement proteins have also been shown to be produced and secreted by airway epithelial cells. C3 was identified as one of the most abundant proteins, along with mucin 5B, mucin 5AC, and fibronectin, in apical secretions from cultures of bronchial epithelial cell lines derived from patients with cystic fibrosis (CF).[5] Factor B was increased, but Factor I was decreased in the CF secretome, as detected by using mass spectrometry–based proteomics. Factor B is a critical enzymatic component of the alternative pathway and promotes inflammation (Fig 1, *A*), whereas Factor I is a fluid-phase serine protease that cleaves C3b to inactivated C3b (iC3b, relative to hemolytic activity) and thus, mitigates inflammation (Fig 1, *B*). Hence, low levels of Factor I could lead to poorly controlled C3 convertase formation, excessive cascade activation, and a potentially heightened airway inflammatory response. Supporting this concept, there was significantly more C3 activation in the CF secretome, as detected by using immunoblotting.[5] Levels of proteases, such as matrix metalloproteinase 9 and cathepsins B and D, were also increased. Whether these proteases are involved directly in cleaving C3 is unknown; however, it suggests that the CF airway epithelial microenvironment can facilitate C3 cleavage *in vivo*.

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OBLITERATIVE BRONCHIOLITIS

Obliterative bronchiolitis (OB) is a form of chronic airway epithelial cell injury that is a predominant manifestation of chronic rejection in patients after lung transplantation and a major impediment to long-term graft survival. Epithelial injury resulting in OB after lung transplantation has been associated with complement-dependent cytotoxicity; however, its precise mechanism is unclear. C3a and C5a upregulate proinflammatory mediators associated with airway epithelial cell injury (Fig 1, *A*).[E34] Conversely, CD55 (decay-accelerating factor) is downregulated on airway epithelial cells of patients with severe asthma in response to injury (viral infection or ozone).[E1] CD55 is a ubiquitously expressed membrane inhibitor that prevents binding of Factor B to the membrane and facilitates decay of the C3 convertase (Fig 1, *B*). CD46 is also a widely expressed membrane regulator and a cofactor for Factor I to inactivate C3b (Fig 1, *B*).[1] Thus, downregulation of these complement inhibitory proteins (CIPs) could lead to poorly controlled airway inflammation and its downstream consequences, such as fibrosis.

Accordingly, reduced expression of CD55 and CD46 was implicated in driving OB after lung transplantation. Both were decreased on the epithelium of patients with OB.[6] These recipients had increased C3a levels in their BAL fluid, indicating C3 activation. In a mouse model in which OB developed at day 21 after lung transplantation, levels of CD55 and Crry (the murine functional homolog of CD46) were decreased in the allograft at day 1, establishing that these changes occurred early. When CD3[1] T cells were cocultured with allograft-specific antigen-presenting cells, C3a increased IL-17a production, which subsequently downregulated Crry. Additionally, treatment with an anti-C5 antibody mitigated OB in mice. This report proposed cross-talk between IL-17a and C3a generation that downregulated CD55 and CD46 expression, thereby increasing the risk of developing epithelial injury and OB after lung transplantation.

INTERSTITIAL LUNG DISEASE

In line with the findings described above in OB, patients with idiopathic pulmonary fibrosis (IPF) had increased C3a and C5a levels in plasma and lung homogenates, leading to speculation that complement is activated both systemically and locally in patients with this irreversible lung disease.[7] In small-airway epithelial cells (SAECs) the fibrogenesis mediator TGF-β induced dose- dependent downregulation of CD55 and CD46 expression. This was associated with increased cleaved poly-ADP ribose polymerase expression, a marker of injury, and a concurrent decrease in E-cadherin, a marker of epithelial-mesenchymal transition (EMT), both of which are hallmarks of IPF. Treatment of SAECs with the anaphylatoxins C3a and C5a at concentrations similar to those identified in the lungs of patients with IPF also resulted in loss of CD55 and CD46, implicating that this downregulation occurred independently with both anaphylatoxins and TGF-β.

The argument for exuberant complement activation in patients with IPF was strengthened by finding increased soluble C5b-9 levels in lung lavage fluid from these patients, suggesting that terminal membrane attack complex formation can mediate cell damage (Fig 1, *A*).[8] In a mouse model of bleomycin-induced lung injury, inhibiting C3aR or C5aR with systemically

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administered antagonists arrested fibrosis by downregulating TGF-β/bone morphologic protein signaling pathways and reducing local complement activation. Of note, this work focused predominantly on C5aR1. Although TGF-β upregulated C5aR2 in SAECs, its role in patients with IPF is still unclear.

These recent reports renew the importance of local complement activation in the respiratory tract. Complement proteins produced by human airway epithelial cells are listed in Table I. Additionally, the complement system does not act independently in the lung microenvironment. There is a bidirectional interaction between complement proteins and other components of the innate immune system, such as antimicrobial peptides (neutrophil-derived α-defensins and human β-defensin 2), that facilitates host defense at the air-liquid interface.[9] An emerging concept for lung disease pathogenesis is that external stress (eg, hypoxia or allergen challenge) or the inherent proinflammatory environment (eg, in those with CF and IPF) increases local synthesis of complement proteins. At the same time, mediators activating the complement cascade also downregulate CIPs, thus putatively propagating ongoing epithelial injury.

Why CIP downregulation is part of the airway epithelial response is puzzling. We speculate that one reason might be that in an acute insult (eg, pneumonia) the airway requires a proinflammatory status to upregulate the complement cascade and downregulate CIPs for the rapid clearing of pathogen or debris. However, chronic complement activation becomes deleterious if this proinflammatory status is prolonged, resulting in irreversible lung disease. Unfortunately, there is no clear evidence that CH50, AH50, and mannose-binding lectin levels are diagnostic biomarkers in any pulmonary disease. Novel therapies targeting locally active complement proteins need to be designed and tested in these difficult-to-treat respiratory diseases to mitigate dysregulation of the complement system.

Although there are no clinical trials currently targeting locally generated complement proteins in the lung, complement inhibitors are now being evaluated for respiratory diseases. These include use of intravenous C1-inhibitor to reduce house dust mite plus LPS–induced bronchial inflammation (NCT03051698, phase IV, recruiting) and use of IFX-1, an anti-human C5a mAb for treating early severe sepsis or septic shock displaying at least 1 newly developed organ dysfunction and showing clinical evidence of pulmonary or abdominal infection (NCT02246595, phase II, completed). A recent review provides a detailed description of historical and current complement-modulating therapies being evaluated in clinical trials.[10]

Additionally, locally delivered complement inhibitors (eg, lampalizumab, a specific inhibitor of Factor D in age-related macular degeneration, NCT02288559) are now being tested. Hence, one approach would be to consider locally delivering already approved specific inhibitors, such as purified C1-esterase inhibitor and anti-C5 mAbs to the lungs (through nebulizers).

Additionally, a relatively unexplored area is enhancing complement regulatory proteins to reduce inflammation, especially in diseases such as IPF and OB that have a known imbalance in regulators. Although recombinant and soluble forms of CD46 and CD55 have

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halted at the preclinical stage in patients with nonpulmonary disease, soluble CR1 was tested in patients with acute lung injury but remains to be evaluated in patients with chronic fibrotic lung injury.[E45] This is an exciting but challenging and rapidly expanding field that now more than ever needs to be better understood and tapped for mitigating lung diseases.

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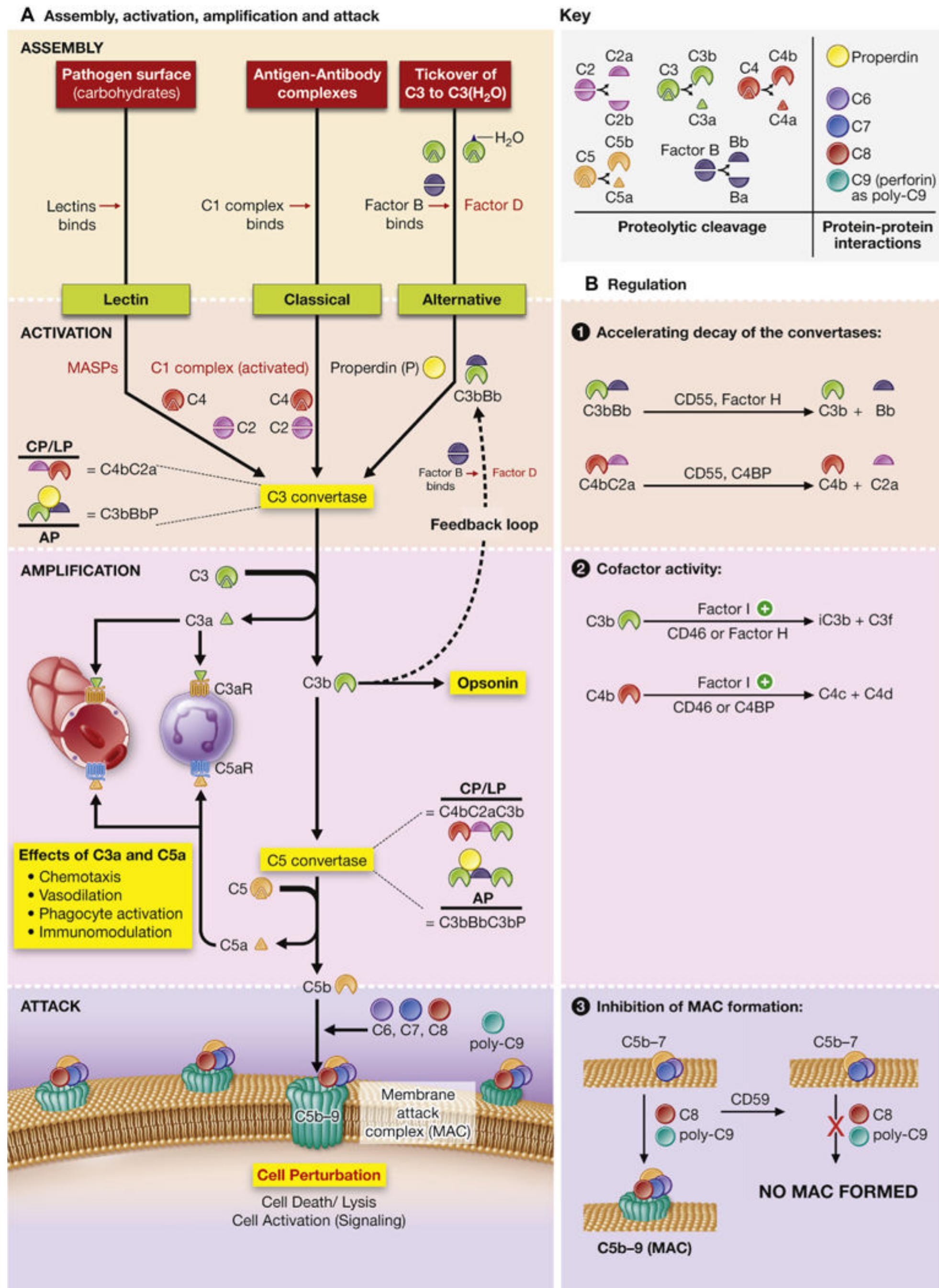

FIG 1.

A, Assembly, activation, amplification, and attack. The complement system is commonly activated by one of 3 triggers. The lectin pathway *(LP)* is triggered when lectins bind carbohydrates (oligosaccharides) on the pathogen surface. Next, mannose-associated serine proteases *(MASPs)* are activated, and they cleave C4 and C2. The classical pathway *(CP)* is triggered by antigen-antibody complexes interacting with the C1 complex *(C1[qr$_2$s$_2$])*. This activates C1s to cleave C4 and C2. The alternative pathway *(AP)* is constitutively active at low levels because C3 metabolizes to C3(H_2O) at approximately 1% per hour. It is amplified

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when C3(H_2O) binds to Factor B and enhanced with binding of the positive regulator properdin *(P)*. Factor B is cleaved by Factor D to Bb, forming C3bBbP. This forms an autocrine feedback loop that can be amplified. All 3 proteases are denoted in red. The 3 pathways converge to form the C3 convertases (formed by enzyme subunits: either C4bC2a for the classical and lectin pathways or C3bBbP for the alternative pathway). The C3 convertases cleave C3 to C3a and C3b. Attachment of C3b to C3 convertases changes their substrate specificity, allowing them to become C5 convertases (C4bC2aC3b or C3bBbC3bP). The C5 convertases cleave C5 to C5a and C5b. C5b then forms the membrane-attack complex with C6, C7, C8, and C9, resulting in cell perturbation. C3a and C5a bind to the G protein–coupled receptors C3aR and C5aR1, respectively, leading to chemotactic, vasodilatory, phagocyte-activating, and immunomodulatory effects. **B**, Complement regulation. The complement cascade is tightly regulated by membrane-associated and plasma proteins to prevent excessive inflammation. CD46 (known as membrane cofactor protein) and CD55 (known as decayaccelerating factor) are membrane regulators, whereas Factor H, Factor I, and C4BP (C4-binding protein) are fluid-phase regulators. CD55 irreversibly decays (dissociates) C2a from C4b, as well as Bb from C3b, to inactivate C3 and C5 convertases. Not shown in the figure is the ability of CD55 to competitively inhibit binding of Bb to C3b and C2a to C4b. Factor H also decays the C3b-containing convertases, whereas C4BP decays the C4b-containing convertases. Factor I proteolytically degrades C3b or C4b but only in the presence of the appropriate cofactors. Complement receptor 1 (*CR1*; CD35) is another membrane-associated receptor and regulator present almost exclusively on hematopoietic cells, which has both decay-accelerating and cofactor activity. CD59 is a membrane regulator that functions independently from CD46 and CD55. It prevents insertion of C8 and C9 into the membrane, thus inhibiting formation of the membrane attack complex and preventing cell perturbation.

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TABLE I

Complement components produced by airway epithelial cells

Components	Evidence	Primary cell data	Tissue data
Classical pathway			
C1q	*Not expressed*[E1]		
C1r	mRNA[E2–E5] Protein[E6]	Zhou et al[E2]	
C1s	mRNA[E3,E7] Protein[E6]		
C4	mRNA[E8–E10] Protein[E6] Supernatant[E11,E12]	Scheetz et al[E9] Walters et al[E10] Peters-Hall et al[E11] Brass et al[E12]	
C2 *	mRNA[E8]		
Lectin pathway			
MBL	mRNA[E5,E13]		Vandermeer et al[E13]
H-ficolin	mRNA[E14] Protein[E14,E15]		Akaiwa et al[E14]
Alternative pathway			
C3	mRNA[E7,E8,E16–E18] Protein[E6,E18,E19] Supernatant[E1,E16,E20,E21]	Ali et al[E20] Pillai et al[E21]	Schlosser et al[E17] Lane et al[E18]
Factor B	mRNA[E8,E13,E16,E17,E22] Protein[E6] Supernatant[E11,E12,E16,E21]	Peters-Hall et al[E11] Brass et al[E12] Pillai et al[E21] Cooper et al[E22]	Vandermeer et al[E13] Schlosser et al[E17]
Factor D	*No data and not expected to occur (primary source: adipocytes)*		
Properdin *	mRNA[E13,E18,E23]		Vandermeer et al[E13] Lane et al[E18]
Terminal complement complex			
C5	mRNA[E7,E8,E17] Protein[E6] Schlosser et al[E17]		Supernatant[E24]

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Components	Evidence	Primary cell data	Tissue data
C6, C7, C8, C9 *	mRNA[E6,E17,E25] Protein[E6]		Schlosser et al[E17] Ying et al[E25]
Regulators, fluid phase			
C1INH	*No data*		
C4BP *	Supernatant[E26,E27]		
Factor H	mRNA[E13,E28] Protein[E6] Supernatant[E21,E28]	Pillai et al[E21]	Vandermeer et al[E13]
Factor I	mRNA[E13] Protein[E6] Supernatant[E21,E26]		
Clusterin	mRNA[E5,E29] Supernatant[E11]	Peters-Hall et al[E11] Hackett et al[E29]	
Regulators, membrane bound			
CD46 (MCP)	mRNA[E26,E30] Protein[E1,E31–E33]		Suzuki et al[E32] Varsano et al[E33]
CD55 (DAF)	mRNA[E34–E37] Protein[E1,E32,E33,E35,E37] Supernatant (shedding)[E36]	Agrawal et al[E34] Pandya et al[E35]	Suzuki et al[E32] Varsano et al[E33] Vainer et al[E37]
CD59	mRNA[E4,E38] Protein[E1,E33,E39] Supernatant (shedding/exosomes)[E12,E20,E40]	Brass et al[E12] Ali et al[E20] Castillon et al[E39] Kesimer et al[E40]	Varsano et al[E33]
Receptors			
C3aR1	mRNA[E41] Protein[E41–E43]	Drouin et al[E41]	Drouin et al[E41] Fregonese et al[E42]
C5aR1	mRNA[E29,E41] Protein[E41–E43]	Hackett et al[E29] Drouin et al[E41]	Gu et al[E43]
C5aR2	*No data*		
CR1 (CD35)	*Not expressed*[E33]		

Components that are not expressed or have no data supporting their production by airway epithelial cells are indicated by italics in the Evidence column. Evidence for protein content was based on immunoblotting, flow cytometry, or mass spectrometry of the cells/cell lysate. *Supernatant* denotes that the cells secreted the protein, unless otherwise specified (in which case it was either shed or secreted as exosomes).

C1INH, C1-inhibitor; *C4BP*, C4b-binding protein; *DAF*, decay-accelerating factor; *MBL*, mannose-binding lectin; *MCP*, membrane cofactor protein.

*Studies from a single research group or conflicting evidence existing in the literature.

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