

Editorial

Stuck in the MUC: Infinity loop of fucosylation in allergic airway inflammation

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Fucosylation is the process performed by fucosyltransferase in which a carbohydrate (fucose), the fucosyl donor, is attached to a hydroxyl or other function group of another molecule, the fucosyl acceptor. Fucose acceptors can be proteins or cell-associated molecules. Glycosylation and fucosylation are important processes: they make proteins more prone to be active, and they can enhance the stability of these proteins and prevent early degradation.¹ Fucosyltransferase 1 and fucosyltransferase 2 (FUT2) are responsible for synthesis of the H (O-secretor) blood group, and they are mediators of inflammatory cell adhesion and angiogenesis.¹

In this issue of the *Journal*, Saku et al² investigate airway epithelial cell (AEC) fucosylation in the context of allergic airway inflammation (AAI). Using lectin microarray screening, they observed fucosylation in AECs in the context of AAI. In the airways lectins functioned as a binding structure for a highly specific sugar moiety. The data showed that AEC fucosyltransferase is a crucial regulator of AAI and that fucosylation serves to mediate communication between epithelial cells, complement, and monocyte-derived dendritic cells (DCs).

Secretion of fucosyltransferase is important because human subjects can have a secretor form of FUT2 SeSe and Sese or a nonsecretor sese form of the *FUT2* gene. This O-secretor is interesting and highly relevant in the context of the article by Saku et al.² In the intestine deficient fucosylation leads to development of colitis/inflammatory bowel disease. In this context intestinal epithelial cell fucosylation appears to be a protective mechanism that uses the host's resources to maintain host-microbial interactions during pathogen-induced stress. In the airway it is more the other way around. If FUT2 is absent from the luminal side of the airways, AAI is reduced.² When asthmatic patients had recurrent exacerbations, they were started on additional therapy to combat the exacerbation. It was found that FUT2 asthmatic patients with the secretor SeSe homozygous or Sese heterozygous genotype performed a lot worse than nonsecretor asthmatic patients with the sese genotype.³

The article by Saku et al² is translational research that applies to the clinical observation of patients with secretor and nonsecretor

genotypes.² The article is important in that it shows how fucosylation operates and why it is important to genotype asthmatic patients at risk (Fig 1, A). It also explains why disease progression occurs in the O-secretor variant of patients with severe asthma,³ even when they are started on progressive anti-inflammatory therapy.

Asthma leads to changes in airway mucus composition.⁴ Epithelial goblet/Clara cell hyperplasia and changes in mucus composition in asthmatic patients are at least in part responsible for impaired mucus ciliary clearance. Mucus plugs (1) contribute to airway obliteration, (2) are a source of recurrent airway infections, and (3) hamper clearance of the airways and resolution of infection.⁵

Almost complete airway obliteration is seen in cases of fatal asthma. Mucus/sputum from asthmatic patients contains anaphylatoxin (C3a and C5a).⁶ In patients with fatal asthma, complement C3a and C5a have been detected in the airway mucosa. Anaphylatoxins are important immune triggers of the innate immune system, and they accelerate the immune response⁵ and serve as an adjuvant (Fig 1, A).⁷ They are also an additional trigger for AAI, especially in the effector phase. This hinders easy resolution of inflammation because the immune system is heavily activated in asthmatic patients. Mast cells and DCs, inflammatory players in asthmatic patients, are activated in a proinflammatory way through complement, and they boost AAI (Fig 1, B).⁷ In general, complement is important, serving as a pathogen recognition pattern for neutrophils in phagocytosis.⁷ In the context of AAI, there is disease progression that results in even more harm to the lungs.⁷ Little is known about how to support resolution of the effector phase in asthmatic patients.⁸ Anti-inflammatory drugs target inflammation in an aggressive way.

A next step in drug research should be toward ways of making structural cells unresponsive to inflammation. Supporting resolution of inflammation is an underdeveloped research area. Little has been discovered about which pathways are important for resolution and how to reshape the immune system to support the function of the shock organ.⁸ It is not known whether and, if so, how the immune system contributes to and prevents repetitive exacerbation. Translational research has shown that targeting complement therapeutically is not the preferred approach because these experiments found no reduction in AAI. The best known approach is to treat asthmatic patients in such a way that asthma symptoms are brought and kept under control by targeting inflammatory cells. DCs are found at pathophysiologically increased levels in asthmatic patients, and they could be additional drivers for the immune response. DCs are not only activated through LPS: complement is also an important trigger for DC activation.⁷ The H antigen associated with glycosylation and coupling of fucose in the mucus kickstart complement activation.

Asthma exacerbation also involves mucus hypersecretion, and as a result of fucosylation, the mucus is immunogenically stronger because of the additional activation of DCs and the T_H2 response, mainly through IL-13, which supports mucus production as a

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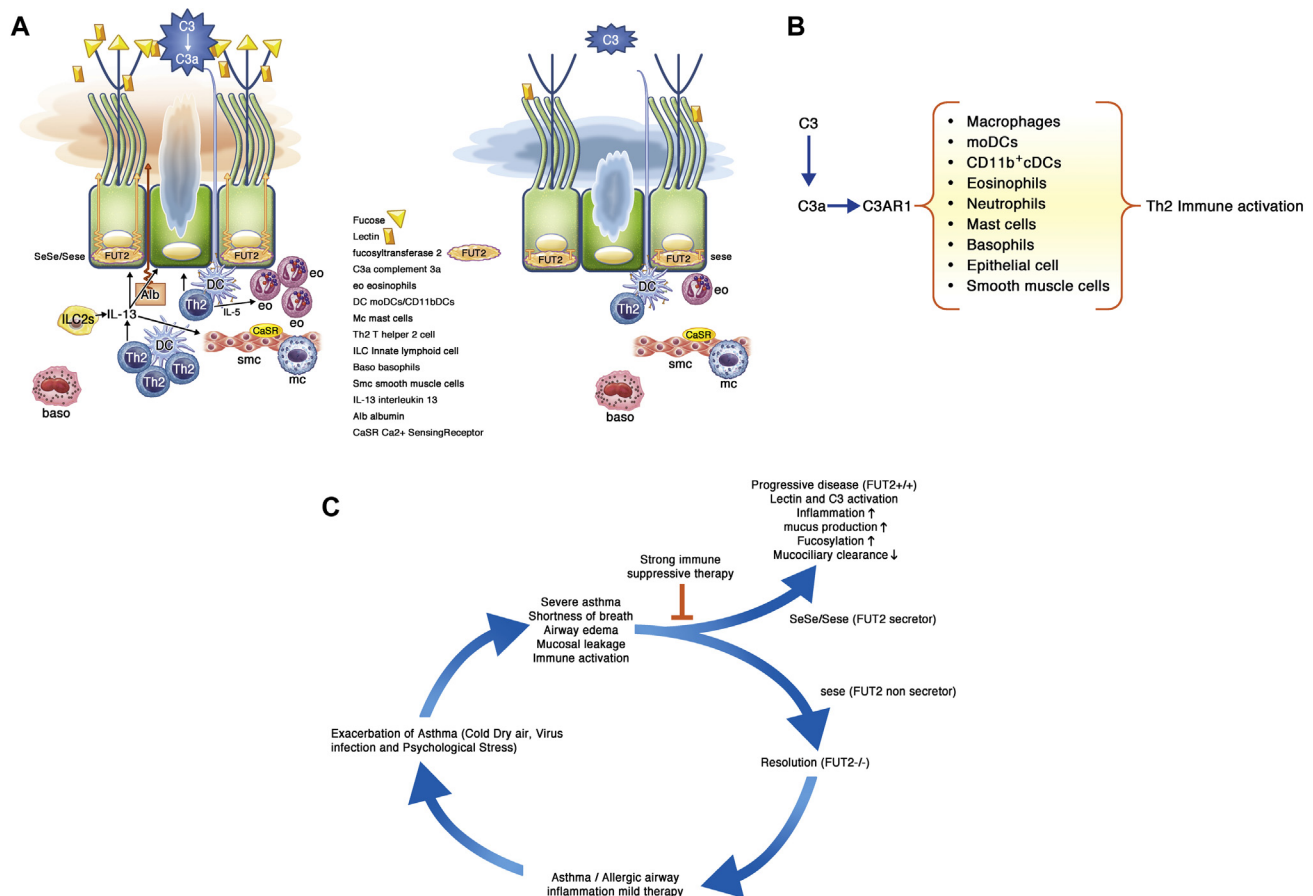


FIG 1. **A**, O-secretor (SeSe or Sese) of fucosyltransferase induces high levels of fucosylation in mucus, resulting in stiff and viscoelastic mucus. Mannose-binding lectin induces complement activation. Complement activation acts as an immunologic trigger for DCs and serves as an adjuvant of the immune response by accelerating and activating T_H2 cells. T_H2 cells and group 2 innate lymphoid cells produce IL-13 and IL-5, which are responsible for mucus hypersecretion, including fucosyltransferase (FUT2). Because of IL-5, eosinophils are recruited, producing all kinds of harmful mediators and resulting in mucosal leakage of albumin and formation of tissue edema. Complement can also activate the mast cells responsible for mediator release and induction of smooth muscle contraction. If FUT2 is not secreted (sese or in mice *Fut2*^{-/-}), there is no complement activation, there is no accelerated immune activation, and immune response can be reduced by regular therapy or by allergen avoidance. **B**, Complement activation is a very broad action because several cells express C3AR1, the receptor for C3a. A very wide range of cells contribute to T_H2 immune activation. *moDCs*, Monocyte-derived dendritic cells. **C**, The loop of AAI if asthma control is lost. It is difficult to slow down the accelerated immune system, and strong adequate therapeutic intervention is needed.

consequence of the immune cascade (Fig 1, C). When mice were exposed to IL-13, the IL-4–IL-13 receptor–signal transducer and activator of transcription 6 pathway was activated, and epithelial cell fucosylation increased. The source of IL-13 is mainly T_H2 cells, group 2 innate lymphoid cells, and mast cells, with the latter being relevant in human asthma only. Fucosylation of mucus component enhances the magnitude of immune responses caused by the combination of complement activation in DCs with the inhaled allergens. Accelerated mucus production is a significant factor that contributes to the risk of asthmatic patients with MUC5AC as a product of airway epithelium and MUC5B as the product of alveolar type 2 cells.^{4,5,7,9,10}

Mucus components, including mucins, such as MUC5AC, are generally fucosylated, leading to extended polymerization of the chain. This has a negative effect on the clearing of the mucus because the sputum of asthmatic patients is highly viscous and

elastic. An effect of *Fut2* is that bronchial hyperreactivity, measured as airway resistance, is less in *Fut2*^{-/-} mice than in wild-type mice treated with house dust mite.² This could be a combination effect of less fucosylated mucins and less stiffness in the mucus in the absence of fucosyltransferase (Fig 1, A). This is of interest because patients with a FUT2 secretor phenotype have more exacerbations.^{3,4} Topical mucolytic or fucosyltransferase inhibitors could be a therapeutic option. MUC5B is the main component of mucus produced in the most distal airway, including the parenchyma type II alveolar cells, and MUC5AC produced by goblet cells and Clara cells is mainly located in the larger airway. Asthmatic patients had increased production of mucus (including MUC5AC), and mucus consistency varied, including production of mucus resulting in mucus plugs, more stiffness, and less clearance because of impaired cilia function. These more structural airway components have never been the focus of primary targets of support

for airway inflammation resolution, and they could be interesting candidates. Flavonoids, glycosides, and steroids, such as natural compounds, can be used in the context of anti-inflammatory and mucus regulatory effects.¹⁰ Therapeutic options that target structural cells (smooth muscle cells, epithelial cells, and endothelial cells) all at once or combined should be investigated. This approach should include at least epithelial cells and endothelial cells by (1) preventing mucosal leakage and tissue edema by supporting tight junctions, (2) supporting mucus cilia clearance through improved cilia function, and (3) making the mucus liquid to reduce viscoelasticity. The physiology of the removal of excessive fucosylated mucus is an important factor that should be improved in asthmatic patients at risk.

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