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To The Editor.

Comment on Review article by Kristina Johansson and Henry McSorley entitled “Interleukin-33 in the developing lung – Roles in asthma and infection.”

In their important review, Johansson and McSorley highlight the features of an upstream epithelial cytokine, IL-33, with instructive roles in TH2 inflammation (1). Emanating from stressed epithelium, IL-33 now attracts major interest as a player in adult asthma including viral infection-evoked exacerbations. However, I find the authors’ discussion of potential involvement of IL-33 in development of asthma in infants in association with RSV infection particularly intriguing.

With reference to work that report increased airway lumen proteins the authors argue that respiratory syncytial virus (RSV) infection disturbs epithelial integrity (1). Yet epithelial integrity may be well maintained in airways exuding proteins. Indeed, in its basic shape increased airways exudation of bulk plasma proteins is a first line innate defence mechanism – it does not derange the epithelial lining and the barrier towards inhaled molecules remains intact (2). Hence, the numerous failures to support the popular idea of increased permeability to allergens etc. in vivo in human asthma (2) are well compatible with the occurrence of plasma exudation in this disease (2).

Here I will mention clear evidence of RSV-induced epithelial derangement. Compelling clinical observations thus demonstrate actual epithelial injury and loss, but only in a

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proportion of RSV-infected infants. Such data become of particular interest in view of epithelial regeneration-evoked airway inflammation and remodelling in vivo.

Creola bodies in airways of RSV-infected infants predicting development of asthma?

Bodies constituted of epithelial cells clumped together and occurring in airway lumen material have been named Creola bodies by Naylor (3) who demonstrated numerous Creola bodies in association with exacerbations of asthma. However, Creola bodies, as a sign of widespread, small patches of epithelial denudation (2), may also be a prominent feature of RSV infection. Indeed, in RSV-infected infants Creola bodies in aspirates may be a prerequisite for the infection to be followed by development of asthma. Yamada et al (4) thus examined occurrence of Creola bodies in infants admitted with acute RSV infection. Only those presenting with Creola bodies in aspirated sputum exhibited a significant risk (relative risk of 3 and 7, respectively) of developing recurrent wheezing and asthma during follow-up at 2 and 5 years. Another study involved 23 hospitalized, wheezing infants with a mean age of about 5 months. They were divided into two groups depending on presence or absence of Creola bodies. In the first month following discharge, asthma symptoms were much higher in the group positive for Creola bodies. Twelve (80%) of these children, but none in the group that lacked Creola bodies, were diagnosed with infantile asthma during a 2-year follow-up period (5). These clinical findings would support the likelihood that IL-33, and other molecules produced in injured and regenerating epithelium, may be involved in asthma development following RSV infections in infants. As noted by Johansson and Mc Sorley, roles of viral infection in inception of asthma have received much attention but data in this field have been inconsistent (1). So the question arises to what extent there is merit in the rarely discussed observations by Yamada et al (4,5) suggesting that a significant risk for development of asthma is confined to those infants who respond to viral infection by exhibiting patchy loss of epithelial cells?

Asthma-like loss of epithelial cells and pathogenic roles of exaggerated epithelial regeneration.

Effects of epithelial loss in vivo have been rarely investigated partly since the common mouse models of asthma lack this feature (2). With guinea-pigs it is different. Allergen challenge of sensitized animals causes epithelial loss at distinct tracheobronchial patches,

which are hot-spots of inflammation and epithelial regeneration (2). Further, experimental removal, in vivo, of airway epithelial cells, without bleeding and leaving an intact basement membrane (as occurs in asthma), results in local asthma-like features, which include: sustained plasma exudation (establishing a provisional fibrinous barrier and a biologically highly active defence and cell regeneration milieu), mucus hyper-secretion, recruitment and activation of granulocytes, proliferation of epithelial and smooth muscle cells, and thickened reticular basement membrane (2).

Beyond participation of all plasma protein systems (2), molecular pathways involved in the pure epithelial regeneration-induced effects listed above have not been determined.

However, it is expected that IL-33 (1) as well as TSLP (thymic stromal lymphopoietin) (6) would be released from such stressed epithelium. Together with other factors, these upstream cytokines are thus contender contributors to an asthma-like state in epithelium-regenerating airways. If epithelial sloughing occurs at numerous sites, epithelial regeneration becomes exaggerated potentially creating a widespread asthma-like state in the tracheobronchial airways, at least transiently (2). It may then be speculated that infants with airways prone to repeat sloughing of epithelial cells in response to RSV infection, as well as in response to other epithelium-damaging culprits, are at particular risk of developing asthma. Additional evidence of epithelial pathology emanates from studies of lethal RSV infections in infants: the airways of these infants have been characterized by pronounced and patchy sloughing of epithelium. Further, sloughed epithelial cells, together with admixed fibrin and mucus, have occluded the bronchial lumen in these cases (7).

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I declare that I have no conflict of interest.

- Accepted Article
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