Airway epithelial cells as guardians of immune homeostasis?

We read with interest the paper by Wang et al and accompanying editorial by Smyth showing that healthy murine airway epithelial cells (AECs) are potent inhibitors of dendritic cell (DC)-induced T cell activation.© AECs infected with respiratory syncytial virus (RSV) lost this regulatory function, allowing activation of T cell responses and airway inflammation.© These in vitro observations match with the high concentrations of pro-inflammatory mediators and cells found clinically in the bronchoalveolar lavage fluid of infants with RSV bronchiolitis.©

The paper by Wang et al adds to a growing body of evidence that AECs are involved in maintaining airway immune homeostasis.© Mayer et al previously showed that primary murine and immortalised human AECs induce an anti-inflammatory microenvironment inhibiting DC maturation and reducing T cell proliferation through constitutive secretion of transforming growth factor-β.©

Wang et al comment that further studies in human primary AECs are required to validate the findings in a clinical setting. Smyth also highlights the importance of research to investigate the function of AECs in health.© Primary AECs cultured from protocol bronchoscopic brushings taken from clinically stable lung allograft recipients free from chronic allograft dysfunction represent a useful model to study AEC function in a healthy, steady state, albeit alloimmune environment. In a recent paper we have shown that epithelial cell-conditioned medium from stable lung allografts drives the production of macrophage-like cells from monocytes rather than DCs.© It is unclear whether this effect only occurs in the airway of lung transplant recipients or if it reflects a genuine culturenegative? It is unclear whether this effect only occurs in the airway of lung transplant recipients or if it reflects a genuine culturenegative? To explore this hypothesis more fully we suggest that future studies should include primary human tissue in both health and disease, and that this strategy can complement and extend animal studies.

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Are patients on treatment for pulmonary TB who stop expectorating sputum genuinely culture negative?

In patients receiving treatment for pulmonary tuberculosis (TB), change in sputum culture from positive to negative is the principal outcome measure of a therapeutic response in both clinical practice and drug trials. Patients will often stop producing sputum early in the course of treatment. We have tested the assumption that “no sputum” means that the patient is “culture negative”, as this has never been confirmed experimentally.

We prospectively followed 16 patients with newly diagnosed pulmonary TB. Sputum samples were collected at diagnosis, during weeks 1 and 2, at months 1, 2, and 4, and on completing treatment. Those patients who were not producing sputum spontaneously had specimens collected by induction. This was performed in a purpose-built negative pressure isolation chamber (Elwyn E Roberts Isolators, Shropshire, UK) where patients inhaled 3% hypertonic saline via an ultrasonic nebuliser for 20 min. Samples were homogenised with Sputasol (Oxoid, Basingstoke, UK). A dilution series

Table 1 Gender differences in health status in patients with chronic cough assessed with the Leicester Cough Questionnaire (LCQ)

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th>Males</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>112 (63)</td>
<td>66 (27)</td>
<td></td>
</tr>
<tr>
<td>Age, years (SEM)</td>
<td>56 (1)</td>
<td>54 (2)</td>
<td>0.5</td>
</tr>
<tr>
<td>Cough duration, years (SEM)</td>
<td>5.5 (0.9)</td>
<td>3.3 (0.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>LCQ total (range 3–21 (SEM)</td>
<td>13.5 (0.4)</td>
<td>14.9 (0.5)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Health status questionnaires are designed to quantify quality of life numerically using the least number of questions. They are not a substitute for taking a good history. During the validation of the LCQ, health-related issues particularly pertinent to females were evaluated. Several items, including stress incontinence, were excluded because only a minority of patients reported them. There was also evidence that alterations in health status due to symptoms such as stress incontinence were adequately captured by items that relate particularly to the psychosocial impact. It is important to note that health status questionnaires should be designed for use in the wider population rather than targeted to a specific subset of patients.

In conclusion, the LCQ is a brief, well-validated and widely used health status questionnaire for patients with cough and can be used to detect gender differences.

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To explore this hypothesis more fully we suggest that future studies should include primary human tissue in both health and disease, and that this strategy can complement and extend animal studies.
Figure 1  Fall in bacterial load (log_{10} cfu/ml) with treatment for (a) patients in group 1 (all samples collected spontaneously; n = 4); (b) patients in group 2 (all samples collected by induction; n = 4); (c) patients in group 3 in whom all induced samples collected after spontaneous sputum stopped were culture negative (n = 6); (d) patients in group 3 in whom two samples collected within the first month of treatment (3.4 log n) were culture positive, after which all samples were culture negative (n = 2). Closed circles, spontaneous samples; open squares, induced samples.

was plated on 7H11 Middlebrook agar made selective with antibiotic tablets (Mycobacteria Selectatabs (Kirchner), MS24 series (Mast Diagnostics, UK)) and the viable colony count was calculated.

The patients were divided into three groups:

- **Group 1**: four patients who produced sputum spontaneously throughout treatment (3 men; median age 47.5 years (range 35–72); 3 Caucasian, 1 Asian; 1 HIV-positive; all sensitive to first-line TB treatment).
- **Group 2**: four patients who never produced sputum and had induced sputum (IS) samples collected throughout (3 men; median age 38.5 years (range 23–51); 2 Black African, 1 Caucasian, 1 Jamaican; 1 HIV-positive; 3 sensitive to first-line TB treatment).
- **Group 3**: eight patients who initially produced spontaneous sputum but underwent IS when this ceased (7 men; median age 31 years (range 17–47); 5 Black African, 2 Caucasian, 1 Asian; 1 HIV-positive; 6 sensitive to first-line TB treatment).

Patients with fully susceptible TB (n = 13) were treated with standard 6-month chemotherapy with a four-drug initial regimen. Five patients with isoniazid-resistant TB received appropriate continuation therapy.

The sputum bacterial load of patients in group 1 became steadily negative during treatment, although they continued expectorating sputum throughout (fig 1a). Patients in group 2 (fig 1b) had a lower initial bacterial load, which also declined to zero on treatment. In group 3, four patients stopped spontaneously producing sputum within 1 month of starting treatment. Six of eight patients had IS samples that were repeatedly culture negative (fig 1c). Only two patients had IS samples that were culture positive; in both cases this was from a single specimen obtained within 1 month of starting treatment (fig 1d). All subsequent IS samples were then culture negative.

Our data suggest that patients on appropriate treatment who stop producing sputum spontaneously are, or will shortly become, culture negative. Performing sputum induction in patients who have stopped producing sputum spontaneously rarely produces a positive result, implying that it should only be performed in patients whose clinical course is uncertain. Cessation of sputum production, especially after 1 month of treatment, appears to be a useful surrogate for culture negativity.

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