15 Grainge CL, Lau LC, Ward JA, *et al.* Effect of bronchoconstriction on airway remodelling in asthma. *N Eng J Med* 2011; 364: 2006–2015.
16 Yamada Y, Yoshihara S, Arisaka O. Creola bodies in wheezing infants predict the development of asthma. *Pediatr Allergy Immunol* 2004; 15: 159–162.
17 Naylor B. The shedding of the mucosa of the bronchial tree in asthma. *Thorax* 1962; 17: 69–72.

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From the author:

Life is short, and the art is long

– Hippocrates

We read with interest C. Persson's letter to the editor. It brings to mind the above quote, as every problem or observation has many potential vantage points. Thus, one's work is never truly finished. In the age of molecular biology, genetics, bioinformatics and systems biology the focus of investigators has naturally shifted to reflect these advances. However, some of the most outstanding discoveries are rooted in earlier observations using *ex vivo* and *in vivo* models of disease.

The commentary by C. Persson is interesting, highly relevant and contains excellent ideas about potential statin epithelial cytoprotective mechanisms. The perspective regarding microcirculation in the rat model, unlike in mice that lack bronchial circulation, is particularly noteworthy. Therefore, on behalf of my co-authors, we appreciate the ideas put forth by C. Persson. We will attempt to address some of the questions raised; and at the end offer a few questions of our own regarding future research directions.

In our study [1], we showed that simvastatin has potent anti-inflammatory effects and prevents tobacco smoke-induced bronchial epithelial denudation. However, our experimental design did not allow us to draw firm conclusions regarding the mechanism(s) underlying these anti-inflammatory and cytoprotective effects. Importantly, we did not assess whether simvastatin's beneficial effects were mevalonate-dependent. Albeit both 1) total cholesterol and 2) small GTPase (Rho and Ras) expression and intracellular localisation did not change (in whole lung homogenate), this does not necessarily indicate mevalonate-independent statin effects.

One potential mechanism for the cytoprotective effect of statins is the induction of pro-resolution and anti-inflammatory factors at the mucosal level. The pro-resolving mediator 15-epi-lipoxin A_4 (15-epi-LXA_4) is important in the resolution of tissue inflammation. Simvastatin and lovastatin both increase the production of 15-epi-LXA_4 in activated human airway epithelial cells [2]. Lovastatin also decreases total and neutrophilic acute inflammation in airway mucosa by increasing the production of 15-epi-LXA_4 *in vivo* [2]. This is likely one of several mechanisms whereby statins protect the airway epithelium, *i.e.* by inducing endogenous pro-resolving mediators during injurious leukocyte–airway epithelial interactions.

C. Persson mentioned that the loss of epithelium may lead to airway inflammation without an inflammatory insult. In our model, smoke exposure induced an acute neutrophilic-predominant inflammatory response and epithelial sloughing throughout the rat bronchial tree. Pretreatment with simvastatin significantly mitigated both of these pathological changes. Whether simvastatin directly prevented epithelial injury due to local cytoprotective effects, or whether simvastatin did this indirectly by reducing leukocyte influx into the airways is not known in our experiments.

In a recent study, JUNCADELLA *et al.* [3] reported that Rac1-dependent defective engulfment of apoptotic airway epithelial cells by neighbouring epithelial cells can lead to increased inflammation. This supports the earlier observation that loss of epithelium and/or improper handling of dying epithelial cells can lead to aberrant anti-inflammatory cytokine production, thereby promoting inflammation. Indeed, knowing this in our model requires different techniques and a more detailed assessment.

Airway microcirculation undoubtedly plays a crucial role in our rat model given that rats, unlike mice, have a bronchial vasculature. Which naturally brings to attention the obvious notion that simvastatin likely had direct, protective vascular or endothelial effects, especially with respect to leukocyte transmigration into airway tissue. The statins have well-documented protective vascular effects affecting an array of biological events important in cardiovascular health and disease.

We also did not discuss airway remodelling because we used an acute 3-day smoke exposure protocol. A current manuscript in preparation documents that simvastatin prevents major hallmarks of adverse airway remodelling in rats after 4 weeks of smoke exposure. Some of the hallmarks mentioned by C. Persson such

as airway thickening, goblet cell metaplasia, epithelial sloughing and repair, and changes in lung function are all addressed in this chronic model of chronic obstructive pulmonary disease (COPD).

We recognise the unmet need for epithelial-active ''cytoprotective'' drugs. Within the context of our work, the statins have been shown to have beneficial epithelial effects [2, 4–9]. There is also a growing interest in evaluating whether statins have direct airway protective effects *via* the inhaled route [10]. Thus, what is the optimal statin route of delivery if we wish to maximise their local airway effects? In humans, statins are only taken orally. Given their protective effects in our COPD model, we wonder whether or not even lower doses of simvastatin can be administered *via* inhalation.

In terms of future directions, the *in vivo* approach will be essential for both mechanistic and therapeutic investigations. Relevant to this field and in particular COPD, three of the most clinically relevant questions are as follows. 1) Is the statin effect additive to that of inhaled corticosteroids? 2) Do statins have a therapeutic role in corticosteroid-resistant hosts? 3) Is the beneficial effect of statins mostly preventative or can statins reverse (or slow down) established airway damage? For the area of statins, the mevalonate pathway and lung biology, it is just the beginning. Indeed, the art is long.

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The statins have protective effects on the airway mucosa that could benefit patients who smoke or those with COPD http://ow.ly/tvy3B

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References

1 Davis BB, Zeki AA, Bratt JM, *et al.* Simvastatin inhibits smoke-induced airway epithelial injury: implications for COPD therapy. *Eur Respir J* 2013; 42: 350–361.
2 Planagumà A, Pfeffer MA, Rubin G, *et al.* Lovastatin decreases acute mucosal inflammation *via* 15-epi-lipoxin A_4. *Mucosal Immunol* 2010; 3: 270–279.
3 Juncadella IJ, Kadl A, Sharma AK, *et al.* Apoptotic cell clearance by bronchial epithelial cells critically influences airway inflammation. *Nature* 2013; 493: 547–551.
4 Zeki AA, Thai P, Kenyon NJ, *et al.* Differential effects of simvastatin on IL-13-induced cytokine gene expression in primary mouse tracheal epithelial cells. *Respir Res* 2012; 13: 38.
5 Murphy DM, Forrest IA, Corris PA, *et al.* Simvastatin attenuates release of neutrophilic and remodeling factors from primary bronchial epithelial cells derived from stable lung transplant recipients. *Am J Physiol Lung Cell Mol Physiol* 2008; 294: 592–599.
6 Marin L, Traini D, Bebawy M, *et al.* Multiple dosing of simvastatin inhibits airway mucus production of epithelial cells: implications in the treatment of chronic obstructive airway pathologies. *Eur J Pharm Biopharm* 2013; 84: 566–572.
7 Sakoda K, Yamamoto M, Negishi Y, *et al.* Simvastatin decreases IL-6 and IL-8 production in epithelial cells. *J Dent Res* 2006; 85: 520–523.
8 Iwata A, Shirai R, Ishii H, *et al.* Inhibitory effect of statins on inflammatory cytokine production from human bronchial epithelial cells. *Clin Exp Immunol* 2012; 168: 234–240.
9 Brandelius A, Mahmutovic Persson I, Calvén J, *et al.* Selective inhibition by simvastatin of IRF3 phosphorylation and TSLP production in dsRNA-challenged bronchial epithelial cells from COPD donors. *Br J Pharmacol* 2013; 168: 363–374.
10 Xu L, Dong XW, Shen LL, *et al.* Simvastatin delivery *via* inhalation attenuates airway inflammation in a murine model of asthma. *Int Immunopharmacol* 2012; 12: 556–564.