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Effect of steroids in asthma

# Blanching the airways: steroid effects in asthma

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## An important effect of steroids on angiogenesis in asthma

The vascular changes which occur in airways diseases such as asthma are starting to attract considerable attention from the respiratory research community. In addition to the vascular engorgement which occurs as part of the acute inflammatory process, several groups have demonstrated increased new vessel formation (angiogenesis) in chronic asthma.<sup>1–3</sup> Not only does this occur in adult asthma, but recent studies suggest it is a prominent feature of childhood asthma, suggesting that vascular remodelling may occur relatively early in the asthmatic process.<sup>4</sup> The increased airway wall thickening produced by the expanded vasculature causes enhanced airway narrowing on stimulation with constrictor agents, thereby contributing to bronchial hyper-responsiveness. Furthermore, the increased blood flow may increase inflammatory cell trafficking and exudation and transudation of cytokines and

mediators and contribute to airway hyper-responsiveness by supporting the increased airway smooth muscle mass which is a key feature of asthma histopathology.<sup>5</sup>

There are a number of candidate angiogenic factors for these changes, perhaps the most important of which are vascular endothelial growth factor (VEGF) and angiopoietin-1, distinct molecules which act together at different stages of angiogenic processes in several biological systems.<sup>6–15</sup> Other molecules with angiogenic potential found in the airways include fibroblast growth factor,<sup>10</sup> angiogenin<sup>10</sup> and chemokines such as interleukin (IL)-8<sup>16</sup> and eotaxin.<sup>17</sup> VEGF is subject to dynamic regulation while angiopoietin-1 is less so, and the latter may contribute in a more permissive way to the remodelling process. A number of stimuli can increase VEGF release from lung cells including cigarette smoke, hypoxia and Th1 and Th2 cytokines such

as IL1 $\beta$ , IL4 and IL13, remodelling cytokines such as TGF $\beta$  and IL6, and vasoactive mediators such as bradykinin and PGE<sub>2</sub>.<sup>18–27</sup> Autocrine production of PGE<sub>2</sub> may mediate the effect of some of these agents,<sup>18, 27</sup> and there is evidence from studies in mouse models to suggest that autocrine nitric oxide production may mediate some (but not all) of the effects of released VEGF in mouse asthma models.<sup>28</sup> Endogenous angiostatic molecules such as endostatin and angiopoietin-2 exert a brake on this process, and the dynamic interplay between these and pro-angiogenic molecules helps shape repair and remodelling.<sup>29</sup>

Interestingly, recent studies in vitro with rhinovirus have shown that infection increases VEGF<sup>30, 31</sup>—but not angiopoietin<sup>30</sup>—release, suggesting a mechanism whereby recurrent viral airway infections might contribute to airway remodelling in a cyclical manner. In mouse asthma models, airway VEGF is increased and VEGF receptor inhibitors inhibit cellular influx as well as inhibiting airway hyper-responsiveness and reducing microvascular leakage,<sup>32</sup> consistent with VEGF having an important deleterious effect in asthma. In these and other studies,<sup>15</sup> VEGF appears to regulate inflammatory processes as well as remodelling, which suggests that it is a complex multifunctional molecule with a wide repertoire of effects. There also appears to be a close relation between VEGF and matrix degradation which probably reflects the fact that establishment of

new vessels requires matrix turnover and that, when the matrix is damaged, new vessels are required for tissue repair.

The study in this issue of *Thorax* by Feltis and colleagues<sup>33</sup> (see page 314) addresses an important issue—namely, whether these angiogenic processes are modified by glucocorticoids. The authors undertook a placebo-controlled intervention study with inhaled fluticasone in 35 patients with mild asthma and performed immunohistochemistry and image analysis to obtain quantitative measures of vessels, angiogenic sprouts, VEGF, VEGF receptor 1, VEGF receptor 2 and angiotensin-1 staining in airway biopsy specimens. They also measured VEGF concentrations in lavage fluid. The key findings were that vessel number, VEGF and sprout staining were decreased after 3 months of inhaled steroid treatment. However, no further reduction was seen at 12 months and relatively high doses of fluticasone were required. Their findings suggest that inhaled steroids downregulate angiogenic remodelling in the airways in asthma, associated with decreasing VEGF activity within the airway wall. Interestingly, VEGF levels in lavage fluid were not altered nor were receptor numbers or staining for angiotensin-1. An interesting finding in this study was the fact that the vascular “sprouts”, which these authors have reported previously,<sup>34</sup> were also reduced by fluticasone treatment. It would seem likely that these cystic structures in the vascular wall of airway vessels may be newly forming vessels.

Glucocorticoids have also been shown to reduce VEGF release in airway cell systems in culture, although their precise mechanism of action has not been established.<sup>35</sup> VEGF regulation is complex and is controlled at both transcriptional and translational levels. Transcription factor binding sites in the VEGF promoter for specificity protein-1 (SP-1) seem to be particularly important, at least in airway smooth muscle,<sup>26</sup> although this has not been studied in other airway cells. VEGF mRNA has regulatory elements in both its 3' and 5' UTR which control its degradation and are potential sites for post-transcriptional regulation.<sup>36</sup> It is not clear whether the effect of glucocorticoids on VEGF production and angiogenesis is mediated by an effect on transcriptional or translational processes.

If glucocorticoids inhibit bronchial vascular changes, what is known about other asthma treatments? Interestingly, long-acting  $\beta$ -agonists have been shown to reduce the vascularity of asthmatic airways in vivo.<sup>1</sup> Although there is some evidence that it might be due to a reduction in VEGF,<sup>35</sup> an alternative explanation

might be a reduction in the level of pro-angiogenic chemokines such as IL8<sup>37</sup> and eotaxin.<sup>38</sup> The leucotriene antagonist pranlukast reduced sputum VEGF levels in a small study of untreated asthmatic subjects but had no additional effect when given concomitantly with inhaled steroids.<sup>39</sup>

Most studies on bronchial angiogenesis to date have used cell culture systems with relevant airway cells in vitro or biopsy studies such as those of Feltis *et al.*<sup>33</sup> Recent reports of new three-dimensional cell culture systems for studying angiogenesis in vitro<sup>40</sup> and reports using magnetic resonance imaging in animal models in vivo<sup>41</sup> might provide additional tools, allowing a greater understanding of this important process over the next few years.

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Bimodality surveillance of high-risk patients for lung cancer

# Bimodality surveillance of high-risk patients for lung cancer

Gordon H Downie

## Are new diagnostic strategies providing answers?

Thoracic oncology providers confronted with the task of diagnosing and following patients at risk for cancer of the lung face a number of major dilemmas, some of which directly affect the ability to diagnose. First, the majority of patients with lung cancer are diagnosed at a late stage and <15% survive 5 years, so a degree of nihilism is present in patients, providers and policy makers. Second, risk paradigms are changing, from smoking only to occupational, environmental or home carcinogens to the risk associated with premalignant airway changes. Third, advances in early diagnostic options have the potential to discover lung carcinoma while still in a pre-invasive, minimally invasive stage or as small peripheral nodules. These points, taken in conjunction with the initial clinical results of the ELCAP study suggesting that cure is possible,<sup>1</sup> raise the need to examine early diagnostic strategies critically.

In this issue of *Thorax* (see page 335) Loewen *et al* report their initial clinical findings in bimodality surveillance of high risk for lung cancer populations using low dose spiral CT scanning (SCT) and autofluorescence bronchoscopy (AFB).<sup>2</sup> They examined two null hypotheses: (1) AFB was equivalent to conventional sputum cytology (CSC) for the detection of pre-malignant lesions and (2) AFB and SCT would be equivalent to SCT alone for the detection of lung cancer

in high-risk patients. The authors conclude that AFB is significantly superior to CSC for the detection of airway pre-malignancy in this cohort of high-risk patients and, in fact, argue that, as a surveillance tool, AFB exceeds the cancer detection rate of colonoscopy in patients with positive fecal occult blood. However, the authors were not able to demonstrate a significant superiority of bimodality surveillance with both AFB and SCT over SCT alone, but question whether a larger sample size would have found bimodality significantly better.

Beyond their null hypotheses, the article raises several points that are healthy components of any discussion of the future approach to patients at high risk of lung cancer. These include:

1. Premalignant changes are common (66% of the 169 patients receiving all components of surveillance) in this high-risk cohort.
2. AFB is reasonable in patients with atypia in CSC; however, CSC was inadequate for detection of pre-malignant cytology when frank carcinoma was not present.
3. Screening and surveillance are very different and surveillance of a select population may be a superior strategy in lung cancer management.
4. Regardless of the histology of the lung cancers detected in this study (>50% were adenocarcinoma), the

majority of patients had central airway pre-malignant transformation.

5. Spiral CT scan protocols are not adequate at this time for detecting central airway disease by themselves.
6. Central airway pre-malignant lesions appear to be predictive of the presence of peripheral adenocarcinoma identified by SCT.

Several of these observations or conclusions have not been supported by other articles in the field. Haubinger *et al*<sup>3</sup> performed a prospective, randomised, multicentre trial comparing white light bronchoscopy (WLB) with or without AFB. The high-risk group defined by chronic obstructive pulmonary disease plus occupational exposure failed to demonstrate severe dysplasia or carcinoma-in-situ (CIS), although it was unclear to what extent metaplasia or mild dysplasia were seen in this cohort. Swensen *et al*<sup>4</sup> and Bechtel *et al*<sup>5</sup> in two separate studies used bimodality testing using CSC as one portion of their testing and suggested a more significant contribution for CSC in lung cancer detection than was suggested by Loewen *et al*.<sup>2</sup> However, because of different study designs including inclusion criteria, biopsy and statistical methods and pathology review variations,<sup>6</sup> it may be nearly impossible to compare findings from one study to another.

Although Loewen *et al* raise several compelling clinical questions in their paper, the most pivotal may well be management issues of airway cellular transformation including dysplasia and CIS. The diagnosis, progression and treatment of dysplasia and CIS, especially in high-risk populations, are demanding more clinical attention to determine surveillance strategies and may affect overall outcomes of lung cancer in the near future. Intense interest in this topic was indicated when most sessions at the 11<sup>th</sup> World Congress on Lung Cancer in