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Epithelial Mesenchymal Transition in Chronic Obstructive Pulmonary Disease, a Precursor for Epithelial Cancers: Understanding and Translation to Early Therapy

To the Editor:

We read with interest the recent editorial by Nichole T. Tanner and colleagues, published in the *AnnalsATS*, considering the lethal association between chronic obstructive pulmonary disease (COPD) and lung cancer that highlighted the potential causal role of epithelial mesenchymal transition (EMT) in this link (1). Understanding these mechanisms is much needed for translation to early, and potentially even preventative, therapy. It is encouraging and reassuring that leading clinical respiratory journals are now recognizing this, as it has been difficult to obtain data on such a novel concept published in high-profile journals.

Human epidemiological studies strongly suggest that patients receiving high-dose inhaled corticosteroids have an appreciable (50%) reduction in the risk for lung cancer (2). We have hypothesized that EMT might be the process through which this effect of inhaled corticosteroids occurs. Thus, in a proof-of-concept randomized controlled trial, we reported that inhaled fluticasone propionate delivered in high doses over the course of 6 months did suppress airway epithelial activation and EMT-related changes in large airways of patients with COPD (3). This was the first study to report anti-EMT effects of inhaled corticosteroids in COPD. If this hypothesis is indeed correct, it has major implications for treating/preventing both obstructive airway fibrosis and lung cancer, although a more safe drug than steroids in these doses would be ideal for long-term use.

We were the first to report that EMT is an active process in both small and large airways of smokers and patients with COPD and was related to reduced lung function in COPD (4, 5). Several other groups have since confirmed these findings. In the large airways, we found that active EMT is present and is associated with hypervascularity of the reticular basement membrane. This gives the typical appearance of active type 3 EMT, which is considered a premalignant condition. It is important to note that it is large airways where most of the squamous cell carcinomas occur, and type 3 EMT could be central to this. The other key pathology associated with COPD is small airway or peribronchiolar fibrosis and obliteration, and this could potentially be related to active type 2 EMT at this site, but fibrosis in general is also associated with malignancy (5).

Very recently, we also reported active EMT in the leading edge of invasive nonsmall cell lung cancer, both squamous and adeno cell types, with the aggressiveness of the tumors being strongly related to the activity of their EMT (6). Further, EMT activity within the tumors closely related to EMT activity in nontumor-affected airway wall epithelium. This work suggests that the level of EMT activity in the airway wall, even in large airways amenable to bronchoscopic biopsy, could potentially be used as a marker for smokers most likely to develop both COPD and lung cancer.

In summary, we appreciate that major journals are beginning to recognize that epithelial activation and basal cell reprogramming with EMT (and epithelially related vessel changes) may represent fundamentally important aspects of COPD pathology, including the severe sequelae of airway fibrosis and cancer development. Indeed, we may now be getting into a position that allows an integrated understanding of this airway disease, with the potential to be translated into a new paradigm for earlier or even preventive therapy, attacking fundamental disease mechanisms rather than symptoms and clinical exacerbations in later-stage patients.

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Unilateral High-Altitude Pulmonary Edema

To the Editor:

We read with great interest the paper by Cherian and Estrada-Y-Martin (1) discussing a case of unilateral pulmonary edema at high altitude.

We have also reported a case of unilateral high-altitude pulmonary edema (HAPE) in a subject with a previously known right pulmonary artery hypoplasia (2). The discussion of our case confirms the theory of overperfusion cited in the Cherian article; in fact, pulmonary edema was limited to the lung without pulmonary artery hypoplasia. Both cases underline the importance of hemodynamic factors in the development of HAPE. There is a strong individual predisposition to HAPE, with a marked pulmonary vascular response to hypoxia and exercise (3). Susceptibility to HAPE is also reported in people with congenital or acquired limitation of the pulmonary vascular bed and/or pulmonary hypertension (3, 4). In these conditions, development of HAPE is possible at an altitude lower than the one related in classical cases (3, 4). Another condition reported as a possible risk factor for HAPE is the presence of a patent foramen ovale (5). Patent foramen ovale is not uncommon, as it is present in approximately 25% of the general population. Some papers suggest that in the presence of patent foramen ovale, sudden ascent to high altitude may create a vicious circle, with the pulmonary hypertension, induced by the hypobaric alveolar hypoxia, leading to a right-to-left shunt that worsens the hypoxemia. In fact, the major determinant of hypoxic vasoconstriction is alveolar hypoxia (6), but systemic and bronchial arterial P_{O_2} and mixed venous P_{O_2} (reduced by exercise in a hypobaric environment) also contribute to a lesser degree and in an additive fashion (6).

Even in the absence of studies specifically assessing the risk, patients with known congenital or acquired conditions that may cause overperfusion and/or hypertension of the pulmonary vascular bed should be advised to take preventive measures before high-altitude travels (3, 4).

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Reply: Unilateral Pulmonary Edema after Visiting High Altitude

From the Authors:

We thank Drs. Fiorenzano and Dottorini for their interest and comments about our article, "Unilateral Pulmonary Edema after Visiting High Altitude" (1) in the Clinical Physiologist section.

We agree that their published report (2), which described the development of unilateral high-altitude pulmonary edema (HAPE) in the setting of right pulmonary artery hypoplasia, is very similar to our case. Their case also reports the development of pulmonary edema in the lung with the normal pulmonary circulation. We agree with them that hypoxia-associated pulmonary vasoconstriction is key to the development of HAPE in susceptible individuals. This is heightened in congenital conditions associated with increased pulmonary blood flow, as