

Pulmonary Hypertension Precedes Emphysema: Paradigm Shift or Artifact of Rodent Studies?

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Editorial

Chronic Obstructive Pulmonary Disease (COPD) is often oversimplified as it was just chronic bronchitis. The patient is such depicted as a constantly coughing and heavily breathing victim of obstructed airways, who will find convenient relieve from bronchodilators. The fact that bronchodilators wear off and that COPD is progressively worsening reminds us of the other definition of COPD which is emphysema, and that this pathology is actually eating up the gas exchanging parts of the lungs, which basically consist of epithelial lined air and blood vessels. The fact that emphysema in contrast to chronic bronchitis is not treatable begs the question whether we have used the right approach for this disease and supports the view that emphysema and chronic bronchitis can be independent diseases.

Two decades ago, Wright and Churg demonstrated in guinea pigs that smoke-induced pulmonary hypertension already occurred before signs of emphysema could be detected [1]. Following this line, researchers have tested around 10 years later the hypothesis that blood vessels are involved in emphysema formation. Their surprising finding was that lung blood vessels are indeed strongly involved in emphysema. A single treatment with the small chemical compound named SU5416, a potent inhibitor of VEGFR2 signaling, which is essential for the survival of vascular endothelial cells, was sufficient to launch a cascade of events leading to lung cell death and emphysema in mice [2]. This ground breaking finding led to the next question: if apoptotic vascular endothelial cell death was important for emphysema development, how could this possibly explain a common feature of pulmonary emphysema, i.e. inflammation? Answering this question was supported by studies, which suggested that in a model of ischemia-reperfusion one molecule, the Endothelial-Monocyte Activating Polypeptide II (EMAPII), was responsible for linking massive apoptotic cells death with inflammation [3]. Indeed inducible and lung specific over expression of secreted EMAPII in transgenic mice was sufficient to cause emphysema-like pathology in mice. Vice versa, nebulization of an anti-EMAPII neutralizing antibody in long term cigarette smoke-exposed mice, which were already progressing toward pulmonary emphysema, was able to stop emphysema development [4].

The identification of endothelial cell death as a main mechanism of emphysema does not stop with this lung pathology. Further animal studies revealed that cigarette smoke-exposed guinea pigs and mice develop vascular remodeling and pulmonary hypertension whereas such alterations preceded the development of emphysema [5-7]. The cigarette smoke-induced vascular pathology is associated with increased muscularization and narrowing of the vessels, endothelial dysfunction and even loss of vessels [6,8]. Although Seimetz et al. were

able to identify inducible nitric-oxide synthase as a joint mechanism underlying both pulmonary hypertension and emphysema the exact mechanism of how pulmonary hypertension precedes emphysema was not addressed yet.

Although the data showing early onset of pulmonary hypertension in mouse models are intriguing, they are in disagreement with the prevailing notion that emphysema precedes pulmonary hypertension, which is believed to result from hypoxia and hypoxemia in the damaged lung with emphysema. However, there is evidence in support of the hypothesis that vascular pathology may even trigger the development of emphysema in humans. In 2002, Santos and colleagues could demonstrate that smokers without deteriorations of the lung function and without emphysema had already manifested pulmonary vascular remodeling [9]. Broader clinical analysis is hampered by the fact that right heart catheterization is not routinely performed in COPD patients. Although, there is awareness that pulmonary hypertension occurs quite frequently in advanced COPD patients [10], the moderate incidence of 30-70% of PH in COPD patients [11] maybe higher when assessed with echocardiography/ultrasound and advanced angiological imaging techniques, e.g. assessment of small pulmonary vessels by chest Computed Tomography (CT) scanning [12]. There is evidence that the presence of even mild PH in COPD is of prognostic relevance [13], but again there is a lack of data in those with beginning or low stage emphysema.

In conclusion, recent mouse study demonstrating that vascular remodeling and PH precede the cigarette smoke-induced emphysema development could clearly show that these effects were hypoxia-independent and gene expression patterns of hypoxia- and smoke-induced PH were quite distinct from each other [6]. The successful prevention of cigarette smoke-induced emphysema in mice by usage of an approved treatment for pulmonary hypertension [14] suggests that targeting the vasculature in beginning pulmonary emphysema may be a promising approach. Further clinical studies monitoring pulmonary hypertension in patients diagnosed with beginning emphysema are required. These studies could be useful to predict who is at risk to progress with or to emphysema.

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