Serotonin: a new start for an old friend?

Aurélie Fabre,1,2 Bruno Crestani1,3

Understanding the mechanisms of fibrotic lung disorders, either idiopathic or associated with a specific aetiology, is the subject of a huge scientific effort in the world, sustained by both the academic pulmonary community and by pharmaceutical companies. The ultimate aim is clearly to identify one or more drugs that will have the capacity to inhibit the decline of lung function and improve survival. Such ambitious goals are unlikely to be reached from one day to another. Rather, we may expect small improvements, perhaps in subgroups of patients, which will add to improve globally the prognosis of this disease process. In the modern era of medicine, in a time in which the transmission of information is rapid and global, such a slow pace of evolution is difficult to accept and certainly contributes to the sense of nihilism sometimes affecting the respiratory community at large, including clinicians, patients and their families, who are challenging fibrotic lung disorders. This negative feeling is also fuelled by the litany of clinical trials in patients with idiopathic pulmonary fibrosis, with negative results (trials evaluating the effect of etanercept,1 imatinib2 or bosentan,3 for example), with conflicting results such as the recent CAPACITY pirfenidone trials,4 or with minimally positive results as with sildenafil.5 Why so many negative results? Before reaching patients, most of these molecules have been tested positive in animal models of lung fibrosis, particularly in the bleomycin-induced lung fibrosis model in rodents. This model is widely used in the scientific community to identify therapeutic targets for treating human idiopathic pulmonary fibrosis, and the question remains whether the model is the right model, or whether we should move to a better model for human disease.6 Because

of the questionable value of that model, it is absolutely necessary to confirm all results obtained in animals by data demonstrated in situ in human lung samples. This is an important point to understand the potential value of the results presented by Konigshoff and colleagues7 in this issue of the journal. These authors should be congratulated for bringing together compelling data supporting the anti-fibrotic action of terguride, a 5-hydroxytryptamine 2A (5-HTR2A) and 5-hydroxytryptamine 2B (5-HTR2B) receptor antagonist. They demonstrated that these receptors are overexpressed in the fibrotic lung in humans, and that this inhibitor limits the development of fibrosis in bleomycin-induced lung fibrosis in mice in vivo and limits the collagen production induced by transforming growth factor beta(1) on human lung fibroblasts in vitro. These results support previous studies published 2 years ago by our group, showing that the pharmacological blockade of either 5-HTR2A or 5-HTR2B reduced bleomycin-induced lung fibrosis in mice and promoted an anti-fibrotic environment by decreasing the expression of profibrotic mediators, namely transforming growth factor beta (1), connective tissue growth factor and plasminogen activator inhibitor 1 messenger RNA, but had minimal effects on lung inflammation as assessed by bronchoalveolar lavage cytology analysis.8 Interestingly, these receptors are widely distributed in the fibrotic lung, as endothelial cells, epithelial cells and fibroblasts (in particular, we observed that fibroblastic foci specifically expressed the 5-HTR2B receptor)9 are positively stained with available antibodies, suggesting that all these cell types could be targets for the drug. As a direct effect of terguride on fibroblasts is demonstrated in the paper by Konigshoff and colleagues,7 it would be very interesting to determine whether 5-HTR2A/2B inhibition could also target alveolar epithelial cells, perhaps by modulating the process of epithelial–mesenchymal transition, which is believed to play a role in lung fibrosis.2 Serotonin (also known as 5-hydroxytryptamine) is a peptide with well-known properties in the lung.10 Serotonin is synthesised from tryptophan and pooled in platelets, which store and release serotonin by its serotonin transporter (5-HTT). Serotonin exerts its action through seven different receptors (5-HT1 to 5-HT7). With the exception of the 5-HT3 receptor, a ligand activated ion channel, all other serotonin receptors are G protein-coupled receptors. Very low levels of circulating free serotonin are detected in normal conditions as serotonin is rapidly degraded by the monoamine oxidase A. In the fibrotic lung, different sources of serotonin may contribute to the local burden of this mediator, platelets obviously, but also neuroendocrine cells11 and mast cells,12 13 which are both increased in the fibrotic lung, and endothelial cells, which have recently been shown to secrete serotonin.14

The demonstration that serotonin is implicated in lung remodelling is not new as serotonin has previously been shown to regulate the remodelling of pulmonary arteries in various forms of pulmonary hypertension,15 focussing either on the role of serotonin receptors16 or serotonin transporters.17 Interestingly, its profibrotic role has also been suggested in the tissue remodelling associated with cancer,18 or in other fibrotic disorders, such as liver fibrosis.19 Altogether, these results suggest that targeting serotonin could bring fresh air to the treatment of fibrotic lung disorders. Is it time for clinical trials?

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