Eur Respir J 2005; 26: 986–988
DOI: 10.1183/09031936.05.00112105

EDITORIAL

Pulmonary arterial hypertension: an autoimmune disease?

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Pulmonary arterial hypertension (PAH) is a rare condition that occurs as a consequence of chronic obstruction of small pulmonary arteries due to endothelial cell, vascular smooth muscle cell and fibroblast dysfunction and proliferation [1]. In recent years, major advances have been achieved in the understanding of PAH pathophysiology [1–7]. It has been firmly demonstrated that pulmonary artery endothelial dysfunction leads to chronically impaired production of vasodilators, such as nitric oxide and prostacyclin, along with overexpression of vasoconstrictors such as endothelin-1 [8–10]. Moreover, genetic studies have shown that germline mutations in the gene coding for bone morphogenetic protein receptor type II (BMPR2) certainly play a critical role in a proportion of patients with familial and idiopathic PAH [2, 3]. Immune disturbances are also believed to contribute to PAH [5]. This is particularly clear in PAH related to connective tissue diseases [5, 11]. In addition, there is a long standing association between autoimmunity and PAH of various origins including idiopathic PAH. However, it remains uncertain how autoimmune mechanisms contribute to the pathogenesis of PAH. In the current issue of the *European Respiratory Journal*, NICOLLS *et al.* [7] review available data documenting the association of autoimmunity and PAH and speculate on the possible role of autoimmune injury in the pathogenesis of the disease.

PAH is a common complication of autoimmune diseases, such as systemic sclerosis (SSc), mixed connective tissue disease and systemic lupus erythematosus [11, 12]. SSc is characterised by excessive collagen deposition in the dermis and internal organs, vascular hyper-reactivity and obliterative microvascular phenomena [13]. Recent studies based on right-heart catheterisation have established that at least 8–12% of SSc patients display PAH [14, 15]. When lung tissue is available, it appears that pulmonary arteriopathy in patients with connective tissue disease-associated PAH has similarities with that described in idiopathic PAH [5, 16]. These resemblances suggest that similar mechanisms may contribute to both conditions. Besides medial hypertrophy, intimal ''onion bulb'' lesions and characteristic plexiform lesion, COOL *et al.* [17] have reported that in patients with SSc-related PAH, mononuclear inflammatory cells surrounded vascular sites of plexiform growth, but not uninvolved vessels or extravascular lung structure. Interestingly, TUDER *et al.* [18] have also reported that perivascular inflammatory infiltrates with macrophages and lymphocytes could be detected in the range of occlusive lesions in idiopathic PAH.

A number of auto-antibodies have been identified in the serum of SSc patients, including disease specific antibodies, such as anti-centromere, anti-topoisomerase 1 and anti-RNA-polymerase Ab. Nonspecific antibodies, such as anti-fibrillarin (U3 small nucleolar RNP), anti-fibrillin 1, anti-Th/To, anti-PM/Scl, anti-mitochondrion, anti-fibroblast and anti-endothelial cell antibodies, have also been identified in the serum of SSc patients [19]. As stated by NICOLLS *et al.* [7], anti-endothelial cell antibodies could play a role in the pathogenesis of SSc, since they can activate endothelial cells, induce the expression of adhesion molecules [20], and trigger apoptosis in the presence of natural killer cells [21]. Moreover, in *in vitro* experiments, auto-antibodies from patients with connective tissue diseases (anti-U1-RNP, anti-dsDNA) induced an upregulation of adhesion molecules (intracellular adhesion molecule-1, endothelial leukocyte adhesion molecule-1), as well as major histocompatability complex class II molecules on human pulmonary endothelial cells, suggesting that such an inflammatory process could lead to proliferative and inflammatory pulmonary vasculopathy [22]. Finally, some patients with severe PAH associated with systemic lupus erythematosus have improved their conditions with immunosuppressive therapy, emphasising the relevance of inflammation and autoimmunity in this subset of patients [23]. However, there are differences in the pathogenesis of idiopathic and connective tissue disease associated PAH that preclude their assimilation. For instance, to date, attempts to detect germline BMPR2 mutations have failed in SSc-associated PAH [24] and the genetic susceptibility of both groups of patients to develop PAH probably differs. Moreover, other investigators speculated that antibodies to BMPRII could trigger PAH in patients with mixed connective tissue diseases. However, these antibodies failed to be detected in any of the patients [25]. Finally, anti-centromere antibodies are associated with the occurrence of PAH in SSc patients, but their pathogenic role is not clearly established.

NICOLLS *et al.* [7] propose that germline BMPR2 mutations might be responsible for regulatory T-cell defects and

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predispose to the occurrence of PAH. Thus, in a manner analogous to patients developing PAH because of acute infarction ramapril emphysema gene mutations [26], they propose that germline BMPR2 mutations may, in part, promote PAH because they lead to a fundamental defect in peripheral immune tolerance and favour the rise of auto-antibodies. This would explain why a significant proportion of idiopathic PAH patients without immunodeficiency or other associated systemic diseases have evidence of autoimmunity and/or active inflammation including detection of circulating auto-antibodies [27, 28]. This autoimmune pathogenetic link is also supported by studies suggesting a close association between idiopathic PAH and autoimmune thyroid disease, including Grave's disease or Hashimoto thyroiditis [29, 30]. Of interest, we have recently reported the presence of anti-endothelial cell antibodies in patients displaying idiopathic PAH [31]. We have observed that immunoglobulin (Ig)G antibodies from patients with idiopathic PAH bind to 36 kDa and 60 kDa bands in endothelial cell extracts with a higher intensity than IgG from SSc patients with PAH and healthy controls. In these experiments, serum IgG from limited cutaneous SSc patients with PAH, but not from idiopathic PAH patients, bound to two major 75 kDa and 85 kDa bands in endothelial cells extracts, suggesting their binding to different target antigens [31]. We recently further identified that IgG anti-fibroblast antibodies are also present in the serum of patients with idiopathic PAH and SSc associated PAH [32]. However, the target antigens, the potential pathogenetic role of these antibodies and their predictive value in patients at risk to develop PAH, such as SSc patients and patients with a familial history of PAH, needs to be investigated. Indeed, the detection of auto-antibodies in a given condition is not sufficient to document an autoimmune mechanism. According to ROSE and BONA [33], different levels of evidence can be obtained to assess the autoimmune nature of a disease. Theses are: 1) direct evidence from transfer of pathogenic antibody or pathogenic T cells; 2) indirect evidence based on reproduction of the autoimmune disease in experimental animals; and 3) circumstantial evidence from clinical clues.

In conclusion, we can easily state here that only circumstantial evidence has been obtained in the case of pulmonary arterial hypertension. Nevertheless, the data reviewed by NICOLLS *et al.* [7] in this issue of the *European Respiratory Journal* plead in favour of the relevance of immune disturbances in pulmonary arterial hypertension of various origins [23], and it is likely that a better understanding of the exact role of autoimmunity and inflammation will help defining novel therapeutic targets in this devastating condition.

REFERENCES

1 Humbert M, Morrell NW, Archer SL, *et al.* Cellular and molecular pathobiology of pulmonary arterial hypertension. *J Am Coll Cardiol* 2004; 43: Suppl. 12, 13S–24S.

2 Lane KB, Machado RD, Pauciulo MW, *et al.* Heterozygous germline mutations in BMPR2, encoding a TGF-beta receptor, cause familial primary pulmonary hypertension. The International PPH Consortium. *Nat Genet* 2000; 26: 81–84.

3 Thomson JR, Machado RD, Pauciulo MW, *et al.* Sporadic primary pulmonary hypertension is associated with germline mutations of the gene encoding BMPR-II, a receptor member of the TGF-beta family. *J Med Genet* 2000; 37: 741–745.

4 Trembath RC, Thomson JR, Machado RD, *et al.* Clinical and molecular genetic features of pulmonary hypertension in patients with hereditary hemorrhagic telangiectasia. *N Engl J Med* 2001; 345: 325–334.

5 Dorfmuller P, Perros F, Balabanian K, Humbert M. Inflammation in pulmonary arterial hypertension. *Eur Respir J* 2003; 22: 358–363.

6 Chaouat A, Coulet F, Favre C, *et al.* Endoglin germline mutation in a patient with hereditary haemorrhagic telangiectasia and dexfenfluramine associated pulmonary arterial hypertension. *Thorax* 2004; 59: 446–448.

7 Nicolls M, Taraseviciene-Stewart L, Voelkel N. Autoimmunity in the pathogenesis of pulmonary hypertension. *Eur Respir J* 2005; 26: 1110–1118.

8 Christman BW, McPherson CD, Newman JH, *et al.* An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. *N Engl J Med* 1992; 327: 70–75.

9 Giaid A, Yanagisawa M, Langleben D, *et al.* Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. *N Engl J Med* 1993; 328: 1732–1739.

10 Giaid A, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. *N Engl J Med* 1995; 333: 214–221.

11 Hoeper MM. Pulmonary hypertension in collagen vascular disease. *Eur Respir J* 2002; 19: 571–576.

12 Simonneau G, Galie N, Rubin LJ, *et al.* Clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2004; 43: Suppl. 12, 5S–12S.

13 Clements PJ. Systemic sclerosis (scleroderma) and related disorders: clinical aspects. *Baillieres Best Pract Res Clin Rheumatol* 2000; 14: 1–16.

14 Mukerjee D, St George D, Coleiro B, *et al.* Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. *Ann Rheum Dis* 2003; 62: 1088–1093.

15 Hachulla E, Gressin V, Guillevin L, *et al.* Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. *Arthritis Rheum* 2005; (In press).

16 Pietra GG, Capron F, Stewart S, *et al.* Pathologic assessment of vasculopathies in pulmonary hypertension. *J Am Coll Cardiol* 2004; 43: Suppl. 12, 25S–32S.

17 Cool CD, Kennedy D, Voelkel NF, Tuder RM. Pathogenesis and evolution of plexiform lesions in pulmonary hypertension associated with scleroderma and human immunodeficiency virus infection. *Hum Pathol* 1997; 28: 434–442.

18 Tuder RM, Groves B, Badesch DB, Voelkel NF. Exuberant endothelial cell growth and elements of inflammation are present in plexiform lesions of pulmonary hypertension. *Am J Pathol* 1994; 144: 275–285.

19 Tamby MC, Chanseaud Y, Guillevin L, Mouthon L. New insights into the pathogenesis of systemic sclerosis. *Autoimmun Rev* 2003; 2: 152–157.

20 Carvalho D, Savage CO, Black CM, Pearson JD. IgG antiendothelial cell autoantibodies from scleroderma

patients induce leukocyte adhesion to human vascular endothelial cells *in vitro*. Induction of adhesion molecule expression and involvement of endothelium-derived cytokines. *J Clin Invest* 1996; 97: 111–119.
21 Bordron A, Dueymes M, Levy Y, *et al*. The binding of some human antiendothelial cell antibodies induces endothelial cell apoptosis. *J Clin Invest* 1998; 101: 2029–2035.
22 Okawa-Takatsuji M, Aotsuka S, Fujinami M, Uwatoko S, Kinoshita M, Sumiya M. Up-regulation of intercellular adhesion molecule-1 (ICAM-1), endothelial leucocyte adhesion molecule-1 (ELAM-1) and class II MHC molecules on pulmonary artery endothelial cells by antibodies against U1-ribonucleoprotein. *Clin Exp Immunol* 1999; 116: 174–180.
23 Sanchez O, Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary hypertension secondary to connective tissue diseases. *Thorax* 1999; 54: 273–277.
24 Morse J, Barst R, Horn E, Cuervo N, Deng Z, Knowles J. Pulmonary hypertension in scleroderma spectrum of disease: lack of bone morphogenetic protein receptor 2 mutations. *J Rheumatol* 2002; 29: 2379–2381.
25 Satoh T, Kimura K, Okano Y, Hirakata M, Kawakami Y, Kuwana M. Lack of circulating autoantibodies to bone morphogenetic protein receptor-II or activin receptor-like kinase 1 in mixed connective tissue disease patients with pulmonary arterial hypertension. *Rheumatology (Oxford)* 2005; 44: 192–196.
26 Korniszewski L, Kurzyna M, Stolarski B, Torbicki A, Smerdel A, Ploski R. Fatal primary pulmonary hypertension in a 30-yr-old female with APECED syndrome. *Eur Respir J* 2003; 22: 709–711.
27 Isern RA, Yaneva M, Weiner E, *et al*. Autoantibodies in patients with primary pulmonary hypertension: association with anti-Ku. *Am J Med* 1992; 93: 307–312.
28 Morse JH, Antohi S, Kasturi K, *et al*. Fine specificity of anti-fibrillin-1 autoantibodies in primary pulmonary hypertension syndrome. *Scand J Immunol* 2000; 51: 607–611.
29 Chu JW, Kao PN, Faul JL, Doyle RL. High prevalence of autoimmune thyroid disease in pulmonary arterial hypertension. *Chest* 2002; 122: 1668–1673.
30 Badesch DB, Wynne KM, Bonvallet S, Voelkel NF, Ridgway C, Groves BM. Hypothyroidism and primary pulmonary hypertension: an autoimmune pathogenetic link? *Ann Intern Med* 1993; 119: 44–46.
31 Tamby MC, Chanseaud Y, Humbert M, *et al*. Antiendothelial cell antibodies in idiopathic and systemic sclerosis associated pulmonary arterial hypertension. *Thorax* 2005; 60: 765–772.
32 Tamby M, Chanseaud Y, Humbert M, *et al*. IgG from patients with pulmonary arterial hypertension (PAH) associated with systemic sclerosis (SSc) and from patients with primary PAH express distinct reactivity profiles with normal human fibroblasts antigens. *Ann Rheum Dis* 2004; 63: Suppl. 1, 346.
33 Rose NR, Bona C. Defining criteria for autoimmune diseases (Witebsky's postulates revisited). *Immunol Today* 1993; 14: 426–430.