Inflammation in Pulmonary Hypertension: How Immunobiology Provides the Missing Link Between These Conditions


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There is an increasing appreciation of inflammation in clinical pulmonary arterial hypertension (PAH). While the controversy remains as to how inflammation may contribute to the pathogenesis of this disease, new avenues of research into this frequently fatal condition are opening as the immune system is being more carefully considered. A variety of diverse inflammatory diseases ranging from viral infections to connective tissue disorders can culminate in pulmonary vascular pathology that is indistinguishable. This review discusses some of the immunobiology that may unite these seemingly unrelated conditions.

Inflammation in PAH has been relatively well described,[1] but whether inflammation is cause or consequence in the pathogenesis of this disease remains undetermined. Severe PAH can be a manifestation of a number of collagen vascular diseases and viral infections. These associated conditions are also either characterized by or have a propensity for autoimmunity. This review will take into account known immune disturbances in PAH and how these events may be early contributors to vascular injury that may contribute to the development of this life-threatening condition.

Pulmonary Arterial Hypertension: Inflammation, Immunodeficiency, and Autoimmunity

Plexiform lesions in PAH lungs are often accompanied by an inflammatory cellular exudate consisting of macrophages, mast cells, and lymphocytes (**Figure 1**).[2-4] Additionally, the presence of antibody-complement deposits have been

Table 1. Viral and Connective Tissue Diseases Associated With PAH

Clinical disease	Autoimmunity observed	Pulmonary hypertension observed	CD4 cell abnormality
HIV infection[39]	Yes	Yes	↓CD4 counts
HHV8 infection[40,41]	Yes	Yes	↓CD4 counts, ↓CD4/CD8 ratio
Hepatitis C infection[42-45]	Yes	Yes	↓CD4 counts, ↓CD4/CD8 ratio, ↓$CD4^+CD25^+$%
Scleroderma[20,46]	Yes	Yes	Normal CD4 counts, ↓$CD4^+CD25^+$%
Systemic lupus erythematosus[47,48]	Yes	Yes	↓$CD4^+CD25^+$%
Antiphospholipid antibody syndrome[21]	Yes	Yes	↓$CD4^+CD25^+$%
Polymyositis[49]	Yes	Yes	↓CD4/CD8 ratio
Hashimoto thyroiditis[50]	Yes	Yes	↓CD4/CD8 ratio
Sjögren syndrome[50]	Yes	Yes	↓CD4 counts

described in several conditions associated with PAH.[5,6] The presence of known systemic autoimmunity in PAH-associated conditions suggests that this inflammation could also impact lung circulation. It has been recognized for more than 40 years that there are associations between autoimmune conditions, such as systemic lupus erythematosus, and severe PAH.

In addition to this well-recognized association with autoimmune disorders, there is a link between viral infections, immune insufficiency, and PAH (**Table 1**). For example, patients who are HIV positive and patients with AIDS are at a higher risk for developing PAH. As with HIV infection, most conditions associated with PAH are associated with a defect in the CD4 T cell compartment, meaning that these conditions are characterized by an absolute deficiency of CD4 cells, a decreased CD4/CD8 ratio, and/or a diminished relative percentage of $CD4^+CD25^+$ cells, the putative regulatory T cell (T_{reg}) subset. Furthermore, PAH has been described following splenectomy.[7] Additionally, it was recently reported that a patient with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), which is caused by a mutation leading to the loss of function of the autoimmune regulator (AIRE) protein, died with fatal idiopathic PAH (IPAH).[8] The AIRE gene is of central importance in the development of thymus-dependent self-tolerance.

Our group has also recently noted that athymic nude rats, which lack T cells, have significantly worse PAH in response to vascular epithelial growth factor receptor antagonism treatment than do euthymic nude rats that have a normal complement of T cells.[9] In this setting of T-cell immunodeficiency, animals develop severe PAH under Denver altitude conditions (ie, chronic severe hypoxia is not required to develop PAH).

It is estimated that 30% to 40% of the patients with IPAH are antinuclear antibody positive, 23% anti-Ku antibody positive, and another 10% to 15% of those patients may express antiphospholipid antibodies.[10-12] A unifying hypothesis that addresses these cumulative findings is that in the setting of relative or absolute immunodeficiency, immune dysregulation likely occurs and may lead to the activation of pathogenic autoreactive B cells and T cells.

Immune Dysregulation in PAH: Lymphocytes, Antibodies, and Mast Cells

Whether injury incurred by T cells or B cells in PAH is important in disease development is currently unknown. However, it is well established, as a general immunologic principle, that in the absence of regulation exerted by a population of regulatory T cells over B cells, autoantibodies will arise and autoimmune disease can develop.[13] With absent or diminished T_{reg} activity, other cells (such as mast cells) presumably provide stimulatory signals to relevant self-reactive B cells, rescue them from apoptosis, and stimulate them to form pathogenic antibodies.[14] Antibodies directed against the vascular endothelium could certainly promote endothelial apoptosis, and antiendothelial antibodies (AECAs) are present in autoimmune disorders associated with PAH including systemic lupus erythematosus,[15] mixed connective tissue disease,[16] and scleroderma.[17] In lupus and Sjögren syndrome, antibody and complement deposits have been localized in the walls of pulmonary arteries of patients with PAH.[5,6]

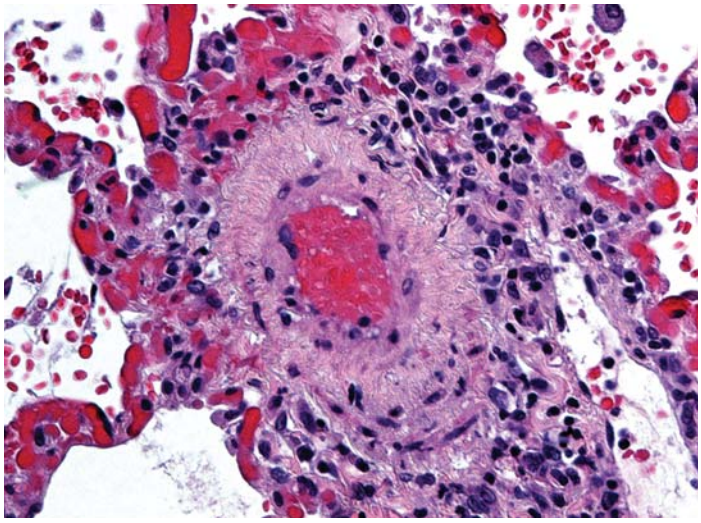

Figure 1. Inflamed arteriole in IPAH patient.

Scleroderma and the antiphospholipid antibody syndrome (APS) are 2 syndromes that may demonstrate how dysregulated immunity can potentially contribute to the development of PAH. Not only are absolute lymphocyte counts reduced in scleroderma,[18,19] but patients with scleroderma also have relatively fewer $CD4^+CD25^+$ cells in the peripheral circulation compared to healthy controls.[20] Similarly, patients with APS have altered peripheral T cell subsets; most notably in a significantly reduced $CD4^+CD25^+$ population.[21] Both conditions are associated with AECAs capable of inducing endothelial cell apoptosis,[22-24] which may be the first event implicated in systemic disease development.[25] An instigating injury to endothelial cells in scleroderma and APS that can trigger autoantibody formation may be a viral infection that leads to immunomodulatory effects.[26-28] In this setting of T_{reg} activity, a dysregulation of B cells is also observed.[29] Plexiform lesions found in the arterial walls of patients with sclerodermal PAH include an inflammatory infiltrate[30] consisting of macrophages, T cells, B cells, and mast cells[31,32]; whereas APS can be associated with pulmonary capillaritis.[33] In summary, scleroderma and APS are disorders characterized by perivascular inflammation associated with possible viral infection, endothelial damage, diminished peripheral $CD4^+CD25^+$ cells, dysregulated B cells, and AECAs. **Figure 2** presents a putative model of this process.

Inflammatory Chemokines and Cytokines in PAH

Inflammatory mediators in patients with PAH are readily detected in the circulation. For example, patients with the syndrome plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes (POEMS) associated with PAH, exhibit increased levels of TNF-α, soluble TNF-receptor type I, IL-2, soluble IL-2 receptor, IL-6, and interferon-Á.[34] Similarly, IPAH patients exhibit markedly elevated IL-1 and IL-6 serum levels.[35]

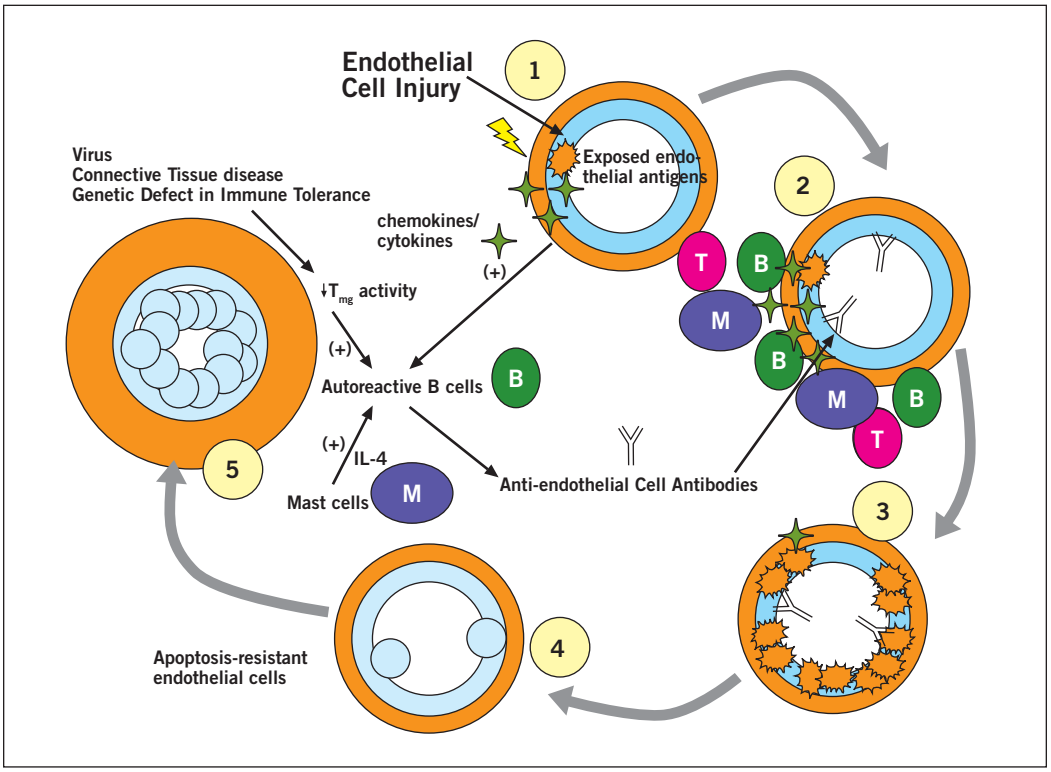

Figure 2. Inflammation in the evolution of pulmonary arterial hypertension: a hypothetical model of disease progression. (1) Injury to vascular endothelium exposes endothelial antigens and increases local chemokine/cytokine concentrations. When the "2 hits" of vascular injury and diminished peripheral immune tolerance occur simultaneously, this may lead to a loss of control normally exerted on autoreactive B cells. (2) Clinical PAH is characterized by B cells, T cells, and mast cells infiltrating plexiform lesions, and antibody-complement deposits that are located in the pulmonary arteries of patients with PAH. (3) Antibody deposition may contribute to ongoing endothelial apoptosis. (4) As a tissue repair response, ongoing endothelial apoptosis results in the generation of apoptosis-resistant endothelial cells that have a malignant phenotype. (5) Apoptosis-resistant endothelial cells become "heaped-up" and begin to occlude the lumen of the vessel, and there is thickening of the vessel wall. The resulting vascular remodeling leads to vascular occlusion, an increased vascular resistance, and worsening of PAH.

FKN/CX3CL1 is a chemokine which is upregulated in CD4+ and $CD8^+$ cells in PAH.[36] Regulated on Activation, Normal T Expressed and Secreted (RANTES, also known as CCL5) is a key cytokine member of the interleukin-8 superfamily of cytokines that is upregulated in the inflammatory milieu of PAH lungs.[37] RANTES is a selective attractant for memory T cells and monocytes that also stimulates endothelin converting enzyme-1 and endothelin-1, a potent vasoconstrictor that may also contribute to increased vascular resistance in PAH.[38] Thus, these cytokines and chemokines in PAH patients may act to further target immune cells to lung circulation.

By focusing on the phenomena of inflammation in PAH, and by incorporating what is known from clinical disease and from experimental models, there should be increasing understanding of how the immune system contributes to this lethal disease. It is conceptually possible that appropriately targeted immunotherapies initiated in a timely fashion will have the potential to attenuate or even reverse this frequently relentless condition.

Acknowledgement

Funding for this review was obtained from NIH HL082662 (MRN) and NIH P01 HL66254 (NFV).

References

1. Dorfmuller P, Perros F, Balabanian K, Humbert M. Inflammation in pulmonary arterial hypertension. *Eur Respir J*. 2003;22:358-363.
2. Heath D. Pulmonary hypertension in pulmonary parenchymal disease. *Cardiovasc Clin*. 1972;4:79-96.
3. 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.
4. Humbert M, Morrell NW, Archer SL, et al. Cellular and molecular pathobiology of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2004;43(12 suppl S):13S-24S.
5. Quismorio FP Jr, Sharma O, Koss M, et al. Immunopathologic and clinical studies in pulmonary hypertension associated with systemic lupus erythematosus. *Semin Arthritis Rheum*. 1984;13:349-359.
6. Nakagawa N, Osanai S, Ide H, et al. Severe pulmonary hypertension associated with primary Sjogren's syndrome. *Intern Med*. 2003;42:1248-1252.
7. Hoeper MM, Niedermeyer J, Hoffmeyer F, Flemming P, Fabel H. Pulmonary hypertension after splenectomy? *Ann Intern Med*. 1999; 130: 506-509.
8. Taraseviciene-Stewart L, Scerbavicius DK, Burns N, Cool CD, Nicolls MR, Voelkel NF. The protective role of T-lymphocytes in pulmonary vascular remodeling. *Chest*. 2005;128(suppl 6):S 571- S 572.
9. 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.
10. 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.
11. Yanai-Landau H, Amital H, Bar-Dayan Y, et al. Autoimmune aspects of primary pulmonary hypertension. *Pathobiology*. 1995;63: 71-75.
12. Karmochkine M, Cacoub P, Dorent R, et al. High prevalence of antiphospholipid antibodies in precapillary pulmonary hypertension. *J Rheumatol*. 1996;23:286-290.
13. Khoruts A, Fraser JM. A causal link between lymphopenia and autoimmunity. *Immunol Lett*. 2005;98:23-31.
14. Tsubata T, Wu J, Honjo T. B-cell apoptosis induced by antigen receptor crosslinking is blocked by a T-cell signal through CD40. *Nature*. 1993;364:645-648.
15. Renaudineau Y, Dugue C, Dueymes M, Youinou P. Antiendothelial cell antibodies in systemic lupus erythematosus. *Autoimmun Rev*. 2002;1:365-372.
16. Sasaki N, Kurose A, Inoue H, Sawai T. A possible role of anti-endothelial cell antibody in the sera of MCTD patients on pulmonary vascular damage relating to pulmonary hypertension [in Japanese]. *Ryumachi*. 2002;42:885-894.
17. Negi VS, Tripathy NK, Misra R, Nityanand S. Antiendothelial cell antibodies in scleroderma correlate with severe digital ischemia and pulmonary arterial hypertension. *J Rheumatol*. 1998;25:462-426.

18. Carapeto FJ, Winkelmann RK. Peripheral blood lymphocyte distribution in scleroderma. *Dermatologica*. 1975;151:228-235.
19. Barnett AJ, Tait BD, Barnett MA, Toh BH. T lymphocyte subset abnormalities and HLA antigens in scleroderma (systemic sclerosis). *Clin Exp Immunol*. 1989;76:24-29.
20. Ingegnoli F, Trabattoni D, Saresella M, Fantini F, Clerici M. Distinct immune profiles characterize patients with diffuse or limited systemic sclerosis. *Clin Immunol*. 2003;108:21-28.
21. Papo T, Piette JC, Legac E, et al. T lymphocyte subsets in primary antiphospholipid syndrome. *J Rheumatol*. 1994;21:2242-2245.
22. Wusirika R, Ferri C, Marin M, et al. The assessment of anti-endothelial cell antibodies in scleroderma-associated pulmonary fibrosis: a study of indirect immunofluorescent and western blot analysis in 49 patients with scleroderma. *Am J Clin Pathol*. 2003;120:596-606.
23. Raschi E, Testoni C, Borghi MO, Fineschi S, Meroni PL. Endothelium activation in the anti-phospholipid syndrome. *Biomed Pharmacother*. 2003;57:282-286.
24. Riboldi P, Gerosa M, Raschi E, Testoni C, Meroni PL. Endothelium as a target for antiphospholipid antibodies. *Immunobiology*. 2003;207:29-36.
25. Sgonc R, Gruschwitz MS, Dietrich H, Recheis H, Gershwin ME, Wick G. Endothelial cell apoptosis is a primary pathogenetic event underlying skin lesions in avian and human scleroderma. *J Clin Invest*. 1996;98:785-792.
26. Harel L, Straussberg R, Rudich H, Cohen AH, Amir J. Raynaud's phenomenon as a manifestation of parvovirus B19 infection: case reports and review of parvovirus
B19 rheumatic and vasculitic syndromes. *Clin Infect Dis*. 2000;30:500-503.
27. Abu-Shakra M, Sukenik S, Buskila D. Systemic sclerosis: another rheumatic disease associated with hepatitis C virus infection. *Clin Rheumatol*. 2000;19:378-380.
28. Ramos-Casals M, Cervera R, Lagrutta M, et al. Clinical features related to antiphospholipid syndrome in patients with chronic viral infections (hepatitis C virus/HIV infection): description of 82 cases. *Clin Infect Dis*. 2004;38:1009-1016.
29. Sato S, Fujimoto M, Hasegawa M, Takehara K. Altered blood B lymphocyte homeostasis in systemic sclerosis: expanded naive B cells and diminished but activated memory B cells. *Arthritis Rheum*. 2004;50:1918-1927.
30. Carreira PE. Pulmonary hypertension in autoimmune rheumatic diseases. *Autoimmun Rev*. 2004;3:313-320.
31. Voelkel NF, Tuder RM. Cellular and molecular mechanisms in the pathogenesis of severe pulmonary hypertension. *Eur Respir J*. 1995;8:2129-238.
32. Harrison NK, Myers AR, Corrin B, et al. Structural features of interstitial lung disease in systemic sclerosis. *Am Rev Respir Dis*. 1991;144(3 Pt 1):706-713.
33. Gertner E. Diffuse alveolar hemorrhage in the antiphospholipid syndrome: spectrum of disease and treatment. *J Rheumatol*. 1999;26:805-807.
34. Feinberg L, Temple D, de Marchena E, Patarca R, Mitrani A. Soluble immune mediators in POEMS syndrome with pulmonary hypertension: case report and review of the literature. *Crit Rev Oncog*. 1999;10:293-302.
35. Humbert M, Monti G, Brenot F, et al. Increased interleukin-1 and interleukin-6 serum concentrations in severe primary pulmonary hypertension. *Am J Respir Crit Care Med*. 1995;151:1628-1631.
36. Balabanian K, Foussat A, Dorfmuller P, et al. CX(3)C chemokine fractalkine in pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2002;165:1419-1425.
37. Dorfmuller P, Zarka V, Durand-Gasselin I, et al. Chemokine RANTES in severe pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2002;165:534-539.
38. Molet S, Furukawa K, Maghazechi A, Hamid Q, Giaid A. Chemokine- and cytokine-induced expression of endothelin 1 and endothelin-converting enzyme 1 in endothelial cells. *J Allergy Clin Immunol*. 2000;105(2 Pt 1):333-338.
39. Zandman-Goddard G, Shoenfeld Y. HIV and autoimmunity. *Autoimmun Rev*. 2002;1:329-337.
40. Parravinci C, Corbellino M, Paulli M, et al. Expression of a virus-derived cytokine, KSHV vIL-6, in HIV-seronegative Castleman's disease. *Am J Pathol*. 1997;151:1517-1522.
41. Kemeny L, Kiss M, Gyulai R, et al. Human herpesvirus 8 in classic Kaposi sarcoma. *Acta Microbiol Immunol Hung*. 1996;43:391-395.
42. Onji M, Doi Y, Miyaoka H, Masumoto T, Horiike N, Ohta Y. Serum levels of soluble CD4 and CD8 in patients with chronic viral hepatitis. *Hepatogastroenterology*. 1994;41:377-379.
43. Boyer O, Saadoun D, Abriol J, et al. CD4+CD25+ regulatory T-cell deficiency in patients with hepatitis C-mixed cryoglobulinemia vasculitis. *Blood*. 2004;103:3428-3430.
44. Eddleston AL. Hepatitis C infection and autoimmunity. *J Hepatol*. 1996;24(suppl 2):55-60.
45. Panasiuk A, Prokopowicz D, Zak J, Wysocka J. Peripheral blood T, B, and NK cells in relation to histological hepatitis activity and fibrosis stage in chronic hepatitis C. *Hepatogastroenterology*. 2003;50:178-182.
46. Degiannis D, Seibold JR, Czarnecki M, Raskova J, Raska K Jr. Soluble and cellular markers of immune activation in patients with systemic sclerosis. *Clin Immunol Immunopathol*. 1990;56:259-270.
47. Crispin JC, Martinez A, Alcocer-Varela J. Quantification of regulatory T cells in patients with systemic lupus erythematosus. *J Autoimmun*. 2003;21:273-276.
48. Liu MF, Wang CR, Fung LL, Wu CR. Decreased CD4+CD25+ T cells in peripheral blood of patients with systemic lupus erythematosus. *Scand J Immunol*. 2004;59:198-202.
49. Benveniste O, Cherin P, Maisonobe T, et al. Severe perturbations of the blood T cell repertoire in polymyositis, but not dermatomyositis patients. *J Immunol*. 2001;167:3521-3529.
50. Covas MI, Esquerda A, Garcia-Rico A, Mahy N. Peripheral blood T-lymphocyte subsets in autoimmune thyroid disease. *J Investig Allergol Clin Immunol*. 1992;2:131-135.
51. Mandl T, Bredberg A, Jacobsson LT, Manthorpe R, Henriksson G. CD4+ T-lymphocytopenia—a frequent finding in anti-SSA antibody seropositive patients with primary Sjogren's syndrome. *J Rheumatol*. 2004;31:726-728.