Primary pulmonary hypertension: the pressure rises for a gene

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Abstract
Primary pulmonary hypertension (PPH) represents the end stage of a disruption of pulmonary vascular integrity, of unknown cause. Although PPH is associated with several systemic disorders, there have hitherto been few clues as to the aetiological factors responsible for the pathogenesis of this condition. As an example of the application of modern molecular genetics and positional cloning, this leader describes the range of studies currently under way, which aim to find the gene that underlies PPH, and summarises the implications of the identification of such a gene.

Keywords: pulmonary hypertension; genetics; chromosome 2q33

Pulmonary arterial hypertension is a devastating disease, characterised clinically by a raised pulmonary artery pressure (mean > 25 mm Hg at rest or > 30 mm Hg during exercise), with normal pulmonary wedge pressure, and subsequent right heart failure. Pulmonary arterial hypertension has been classified as: (1) primary pulmonary hypertension (PPH), of unknown cause, which is either sporadic or familial (at least two family members); (2) related to other conditions such as human immunodeficiency virus (HIV) infection and ingestion of appetite suppressants. There are many secondary causes of raised pulmonary artery pressure, including chronic obstructive pulmonary disease and thromboemboli, which are listed fully in table 1, in accord with the 1998 World Health Organisation classification of pulmonary hypertension. This review will focus on our present understanding of the clinical and molecular genetics of PPH and its relation to other forms of pulmonary arterial hypertension.

PPH has a reported incidence of one to two new diagnoses/million/year in developed countries and is twice as common in women as in men, although it has a similar disease progression in both sexes. The mean age of onset is 36.4 years but it can occur at any stage of life and it has a median survival time of 2.8–3.4 years from diagnosis. Diagnosis of the disease can be lengthy, in part because of the non-specific presentation with breathlessness and fatigue, few clinical signs, and the numerous tests required to exclude secondary causes of pulmonary hypertension. Treatment is based on calcium antagonists and anticoagu-

Table 1  WHO classification of pulmonary hypertension

1. Pulmonary arterial hypertension
   1.1 Primary pulmonary hypertension
      (a) Sporadic
      (b) Familial
   1.2 Related to
      (a) Collagen vascular disease
      (b) Congenital systemic to pulmonary shunts
      (c) Portal hypertension
      (d) Human immunodeficiency virus infection
      (e) Drugs/toxins
         (1) Anorexigens
         (2) Other
      (f) Persistent pulmonary hypertension of the newborn
      (g) Other
   2. Pulmonary venous hypertension
      2.1 Left sided atrial or ventricular heart disease
      2.2 Left sided valvular heart disease
      2.3 Extricin compression of central pulmonary veins
         (a) Fibrosing mediastinitis
         (b) Adenopathy/tumours
      2.4 Pulmonary veno-occlusive disease
      2.5 Other
   3. Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxaemia
      3.1 Chronic obstructive pulmonary disease
      3.2 Interstitial lung disease
      3.3 Sleep disordered breathing
      3.4 Alveolar hypovenion disorders
      3.5 Chronic exposure to high altitude
      3.6 Neonatal lung disease
      3.7 Alveolar capillary dysplasia
      3.8 Other
   4. Pulmonary hypertension as a result of chronic thrombotic and/or embolic disease
      4.1 Thromboembolic obstruction of proximal pulmonary arteries
      4.2 Obstruction of distal pulmonary arteries
         (a) Pulmonary embolism (thrombus, tumour, ova and/or parasites, foreign material)
         (b) In situ thrombus
         (c) Sickle cell disease
      5. Pulmonary hypertension as a result of disorders directly affecting the pulmonary vasculature
         5.1 Inflammatory
            (a) Schistosomiasis
            (b) Sarcoidosis
            (c) Other
         5.2 Pulmonary capillary haemangiomatosis

Clinical genetics of familial PPH
Dresdale first described PPH in 1951, and its heritability in 1954. Although most cases are apparently “sporadic”, one series showed that 6% of patients have at least one other family member with the condition. We have now identified 21 affected families throughout the UK. Over 100 families have been recognised in the USA with further kindreds described in Europe, Japan, and Australia.

Clinical studies of families with PPH have revealed several important features. Many examples of male to male transmission of PPH have been cited, excluding X linked inherit-
Figure 1. Familial primary pulmonary hypertension (PPH). A hypothetical pedigree illustrating reduced genetic penetrance of the disease (that is, skipping of generations) as seen in individuals II-2 and III-2. “Anticipation” (earlier age of onset in successive generations) and the female preponderance. Open square, unaffected male; open circle, unaffected female; closed square, affected male; closed circle, affected female; slash, deceased.

Figure 2. Idiogram of the long arm of chromosome 2 (2q). The PPH1 gene location showing genetic markers D2S335 and D2S369 and the reduction of the critical interval from 25 to 6 centimorgans (cM).
Pathobiology of PPH providing genetic clues

PPH is associated with narrowing of the precapillary pulmonary arteries, reflecting endothelial and smooth muscle cell proliferation, pronounced vasoconstriction, and in situ thrombus formation. Abnormal expression of ion channels, altered concentrations of vasoactive mediators, aberrant vascular remodelling in response to haemodynamic change, and pulmonary artery endothelial and smooth muscle cell dysfunction may each underlie the molecular mechanisms generating the pathological cascade. The observed increase in endothelin-1 expression (vasoconstrictor), in combination with reduced urinary excretion of prostacyclin metabolites and endothelial nitric oxide synthase expression in pulmonary arteries of patients with PPH (vasodilators), provides a scientific basis for vasodilator treatment in this disease.

Cytosolic free calcium acts as an important regulator of smooth muscle contraction and cell proliferation. Yuan et al have shown that the opening of voltage gated potassium (Kᵥ) channels in pulmonary artery smooth muscle cells of patients with PPH is inhibited, causing membrane depolarisation and a rise in cytosolic calcium, and hence vasoconstriction (fig 4). Kᵥ channels are composed of pore forming α subunits (for example, Kᵥ1.5) and cytoplasmic regulatory subunits (for example, Kᵥ1.1). In PPH, Kᵥ1.5 mRNA is reduced in comparison with normal and secondary pulmonary hypertension controls. Although the gene encoding Kv1.5 is not itself within the PPH1 critical interval, the PPH gene might still be involved with the regulation of these channels.

Further studies of Kᵥ channels have exploited the association of ingestion of phenylethylamine based appetite suppressants and the development of pulmonary hypertension. The incidence of pulmonary hypertension in Europe escalated in the 1960s after the release of amphetamine-based appetite suppressants and the development of pulmonary hypertension. The incidence of pulmonary hypertension in Europe escalated in the 1960s after the release of amphetamine-based appetite suppressants and the development of pulmonary hypertension. The incidence of pulmonary hypertension in Europe escalated in the 1960s after the release of amphetamine-based appetite suppressants and the development of pulmonary hypertension.

Use of these amphetamine-like drugs for more than three months is associated with a 3.1-fold increased risk of developing pulmonary hypertension, which is clinically and histologically indistinguishable from PPH. Wang et al have demonstrated reduced expression of the Kᵥ1.5 α subunit in human normotensive pulmonary artery smooth muscle cells after the addition of fenfluramine, supporting a proposal that anorectics might cause pulmonary hypertension through their effect on Kᵥ channel gene regulation.

Further pointers to the genetic basis of PPH have come from clonality studies of the characteristic plexiform lesions. Plexiform lesions are composed of abnormally large endothelial cells seen at pulmonary vessel bifurcations. Voelkel et al examined 22 plexiform lesions from patients with PPH and 20 from patients with secondary pulmonary hypertension. At the time of reporting, there were strong indications that most plexiform lesions from patients with...
Smooth muscle cell potential depolarisation, a rise in intracellular calcium, and vasoconstriction.

Figure 4 Inhibition of voltage gated potassium channels in pulmonary artery smooth muscle cells of patients with primary pulmonary hypertension (PPH) causing membrane depolarisation, a rise in intracellular calcium, and vasoconstriction.

PPH were monoclonal in origin. Conversely, all plexiform lesions from patients with secondary pulmonary hypertension displayed polyclonal proliferation. These results indicate autonomous growth of endothelial cells in PPH, similar to tumorigenesis and that seen in smooth muscle cells of atherosclerotic plaques, perhaps through abnormal regulation of a gene controlling cell growth.

This finding has also provoked a “two hit” theory for the molecular development of PPH. In this model, genetic mutations would need to occur on both copies of a PPH gene, as seen with Knudson’s two hit hypothesis and the inheritance of retinoblastoma. Here, in individuals with familial PPH, one mutation would have to be inherited in the germ line, and exposure to an environmental stimulus would provide the second “somatic” hit in a cell causing monoclonal growth.

Other associated diseases

In 1987, Kim and Factor described the first case of HIV associated pulmonary hypertension. By 1997, 88 patients with HIV or AIDS had been described in whom pulmonary hypertension had developed, 42% having previously used intravenous drugs, and with no hypertension had developed, 42% having previously used intravenous drugs, and with no hypertension had developed, 42% having previously used intravenous drugs, and with no hypertension had developed, 42% having previously used intravenous drugs, and with no hypertension had developed, 42% having previously used intravenous drugs, and with no hypertension had developed, 42% having previously used intravenous drugs, and with no hypertension had developed, 42% having previously used intravenous drugs. More than 20 000 people suffered acute pneumonitis, myalgias, and eosinophilia, with 20% developing pulmonary hypertension. The pulmonary hypertension regressed in all but 1.5% of patients up to four years after the initial illness. In those whom pulmonary hypertension progressed, the clinical and histological findings were indistinguishable from PPH. Some of the puzzles surrounding the toxic oil syndrome may be answered through identification of the PPH1 gene, as with HIV infection and appetite suppressants. Those individuals developing persistent pulmonary hypertension subsequent to an environmental agent might only do so if they are genetically susceptible.

Future prospects

Identification of the PPH1 gene will herald a new era of pulmonary vascular biology research. Prospects for the future include the development of more specific and effective treatments, leading to improvement in disease prognosis. In families with PPH, presymptomatic genetic testing will highlight those relatives requiring clinical screening, with the potential benefits of early treatment and avoidance of pregnancy (which may precipitate PPH), environmental “triggers”, and hypoxic environments. In those who have developed pulmonary hypertension following the ingestion of appetite suppressants, toxic oil, and HIV infection, it will become possible to establish whether they have a similar genetic susceptibility, which should prompt further investigation of gene–environment interactions. Through the study of familial PPH a greater understanding of other forms of pulmonary hypertension is likely to follow.

The authors gratefully acknowledge the generous support of those with PPH and their families who have contributed to the studies referred to in this article, and funding by the British Heart Foundation (project grant: RCT) and Medical Research Council (MRC clinical training fellowship: JT).