Short Communication

Neointima Development in Pulmonary Arterial Hypertension: A Possible Mechanism

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ABSTRACT

Pulmonary arterial hypertension (PAH) is a significant complication of a variety of systemic disorders, such as cardiac, inflammatory, and autoimmune diseases. Endothelial instability and dysfunction are important in the onset and course of the disease. Although current medicine has improved quality of life, the underlying vascular disease continues to worsen, and the survival rate has not considerably improved. Impaired vascular relaxation response, medial hypertrophy, and increased pulmonary pressure are the predominant pathogenic alterations; subsequent neointimal development resulting in disease irreversibility. The loss of endothelial Caveolin-1 (cav-1), a membrane protein, has been linked to the reciprocal activation of proliferative pathways and the onset of PAH. Endothelial cell and endothelial cav-1 disruption is followed by increased expression of cav-1 in smooth muscle cells.

Keywords: Injury; Pulmonary arterial hypertension (PAH)

Introduction

In 1891, Ernst von Romberg used the term "pulmonary vascular sclerosis" to describe histological abnormalities in the lungs, which is widely regarded as the earliest description of pulmonary hypertension (PH). Dyspnea, cyanosis, right ventricular failure, and pulmonary vascular sclerosis were identified by Abel Ayerza in 1901. For a long time, the sickness was referred to as "Ayerza's disease" [1,2]. Although great work has been made in the research since then, the mechanism(s) of PH remain unknown. PH has been linked to a variety of systemic ailments, including cardiac, systemic, infection, inflammatory and autoimmune diseases, haematological disorders, and medication toxicity. The classification of PH into five primary clinical classes was modified in 2013 [3]. Pulmonary Arterial Hypertension (PAH) is classified into two groups: idiopathic and heritable PAH, as well as PAH caused by a congenital heart defect, drug toxicity, inflammation, and autoimmune illnesses. Without treatment, PAH patients have a 2.8-year survival rate [4]. Although modern therapy has improved quality of life, the underlying vascular disease continues to worsen. The one-year survival rate for PAH patients is 85%, while the three-year survival rate is 58%. When the mean pulmonary artery pressure is >25 mmHg, the pulmonary capillary wedge pressure is 15 mmHg, and the pulmonary vascular resistance is >3 Wood units at rest, PAH is diagnosed. The loss or increased expression of molecule/s as a result of an injury disrupts the delicate network of signalling pathways, resulting in a dysregulated inflammatory response, cell proliferation, cell migration, and angiogenesis, all of which contribute to PAH development and progression. Medial hypertrophy, cellular intimal proliferation, concentric laminar intimal fibrosis, fibrinoid necrosis, dilatation lesions, and plexiform lesions are the stages of PAH. The pulmonary vascular lesions were also observed to be similar to primary pulmonary hypertension and PAH associated with a congenital heart defect [5]. The pulmonary vascular alterations in children with congenital heart defects (left to right shunts) who had pulmonary artery banding to restrict pulmonary flow were reversed. Early

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intimal alterations and medial hypertrophy looked to be reversible, but the latter stages were not. PH is characterised by

- endothelial dysfunction/ disruption, which results in impaired vascular relaxation and activation of proliferative and antiapoptotic pathways;
- smooth muscle cell proliferation, medial thickening, lumen narrowing, and elevation of pulmonary artery pressure, regardless of the underlying disease; and
- right ventricular hypertrophy. SMC phenotype changes from contractile to synthetic as disease develops, and they contribute in cell migration and neointima development, resulting in arterial occlusive disease, RV failure, and early mortality. The creation of neointima causes the condition to become irreversible.

To maintain homeostasis, a huge number of signalling molecules in the pulmonary vasculature interact intricately. PAH is caused by a combination of variables that are out of whack. Endothelial dysfunction, impaired vascular dilatation, changes in NO, ET1, and serotonin levels, increased expression of inflammatory cytokines and chemokines, and disrupted extracellular matrix proteolysis all play a role in the pathophysiology of PAH. In addition, perivascular infiltration with inflammatory cells (T and B cells) has been documented in plexiform lesions [6]. VEGF, EGF, TGF beta, MMPs, BMPR2, and Notch, as well as an imbalance of vasoactive mediators and vascular remodelling, abnormalities in ion channels (Ca^{2+},K^{+}), and growth factors such as VEGF, EGF, TGF beta, MMPs, BMPR2, and Notch, have all been implicated in the aetiology of PAH. There are no animal models that accurately represent PAH in humans. This is unsurprising given that PAH is caused by a variety of unrelated disorders. Furthermore, in animal models, species differences might influence pathological modifications, and the results are influenced by the length of the research and the rate at which pathological abnormalities in the vasculature occur. Despite these drawbacks, animal models of PH have made significant contributions to our understanding of the disease. The diagnosis of PAH is frequently delayed due to a lack of specific symptoms, and early pathological changes are not clinically discernible. Significant molecular and clinical changes have been found to occur before the development of PH in an animal model of PH.

Pulmonary Hypertension Models

To induce PH in animals, Monocrotaline (MCT), a poisonous pyrrolizidine chemical derived from the seeds and leaves of Crotalaria Spectabilis, has been employed. Cytochrome 450 in the liver converts MCT to Dehydromonocrotaline (DHMC). In rat serum, DHMC has a half-life of roughly 5 seconds. A big dose causes immediate liver damage and death in a matter of days. A tiny dose causes transitory liver injury, and DHMC destroys endothelial cells during the initial passage through the lungs, causing pulmonary vascular alterations. Rats with MCT-induced PH are a well-studied model. Before the onset of PH, a single 60 mg/kg sc injection causes progressive endothelial disruption and endothelial caveolin-1 (cav-1) loss in rats, as well as reciprocal activation of proliferative and anti-apoptotic pathways such as PY-STAT3, and Bcl-xL [7]. Endothelial cav-1 loss is accompanied by the loss of other membrane proteins such as Tie2, PECAM-1, soluble guanylate cyclase (and), indicating a broad endothelial membrane breakdown. At 2 weeks after MCT, there is a further decrease of endothelial cav-1, as well as PH, right ventricular hypertrophy, and NF-B activation. At this time, there is also a considerable drop in the expression of various cytosolic proteins such as I-B, HSP90, Akt, protein-bound sulfhydrils, and cGMP levels. At 2 weeks and 4 weeks post-MCT, MMP2 expression and activity are gradually increasing. In addition, the MCT model has been shown to promote collagen and insoluble elastin synthesis. However, no evidence of neointima development has been seen in MCT-treated rats.

Because the dog liver lacks the enzyme that converts MCT to DHMC, Dehydromonocrotaline (DHMC) has been used as an intra-atrial injection to induce PH in dogs. Beagle dogs (age 12 weeks) exhibited substantial PH, pulmonary vascular remodelling, including medial wall and adventitial thickening and neointima development, and right ventricular hypertrophy eight weeks after receiving an intra-atrial injection of DHMC (3 mg/kg) [8]. Adult mongrel dogs given a DHMC (3 mg/kg) injection also developed PH, thickened medium-sized

arterioles, and destroyed tiny arteries. It's worth noting that whereas neointima development has not been found in rats, neointimal lesions have been described in dogs following DHMC injection. Because the dogs were tested eight weeks after receiving the DHMC injection and the rats are normally checked two to four weeks after receiving the MCT injection, the duration of endothelial disruption and elevated pressure is likely to play a role in the development of neointima. Although MCT alone did not cause neointima formation in rats, a second hit such as increased pulmonary blood flow or hypoxia caused neointima formation.

In addition to MCT-induced endothelial injury and PH, increased blood flow has been found to cause neointima development. The right pulmonary artery remodelling in MCT with pneumonectomy animals was compared to MCT or pneumonectomy animals alone. More than 90% of all right lung intra-acinar arteries had neointimal alterations 5 weeks following MCT injury (4 weeks after pneumonectomy). Untreated animals and those who just received MCT or pneumonectomy did not develop neointimal lesions. When compared to control mice, animals with a neointimal pattern of remodelling developed severe RVH, whereas animals with a medial hypertrophic pattern of remodelling (MCT alone group) produced moderate RVH. In addition, increased oxidative stress, increased production of cytokines and NOX4 and MnSOD, infiltration of the pulmonary arterial wall with inflammatory and CD68+/vimentin+cells, and infiltration of the pulmonary arterial wall with inflammatory and CD68+/vimentin+cells were detected [9]. A week before MCT injection, an abdominal aorto-pulmonary shunt was done; 4 weeks-5 weeks later, higher mortality and neointimal lesions were found. Increased pulmonary blood flow in the context of compromised endothelium causes significant pulmonary vascular alterations, according to these investigations.

When MCT-injected rats are exposed to hypoxia, the disease process and the creation of neointima is accelerated. The neointimal lesions were stained positive for -actin but not vWF, indicating SMC migration into the neointima. In SMC, there was a significant decrease of endothelial cav-1 and an increase in cav-1 expression. Only arteries with substantial endothelial cav-1 loss at 4 weeks show increased expression of cav-1 in SMC. Furthermore, neointimal lesions were only found in arteries with significant endothelial cav-1 loss and increased cav-1 expression in SMC. Importantly, similar changes in human PAH were identified. In an in-vitro research, SMC from individuals with idiopathic PAH demonstrated increased expression of cav-1, increased capacitative Ca^{2+} entry, and increased DNA synthesis, all of which could be prevented by silencing cav-1.

The VEGF receptor blocker Sugen 5461 was used to cause PAH. Sugen was injected into rats, who were subsequently exposed to hypoxia for three weeks before being returned to a normoxic environment. Polycythemia returned to normal following exposure to normoxia, PAP dropped somewhat, but vascular alterations persisted, and plexiform lesions appeared 13 weeks-14 weeks after sugeon injection. Surprisingly, wearing a unilateral PA band prevented and reversed pulmonary vascular alterations [10]. Endothelial injury in the context of increased pressure/flow resulted in gradual vascular alterations, according to these research.

Neointima Formation: A possible Mechansim

Endothelium is a semi-permeable membrane that serves as a barrier between the media (smooth muscle cells) and circulation. It maintains a balance between constriction and dilation of the blood vessels, as well as cell proliferation and death. It also serves as a barrier, balances pro- and anticoagulant factors in the vessel wall, and contributes to immunological function. Caveolae, rich in cholesterol and sphingolipids, are specialised microdomains in the plasmalemmal membrane of endothelial cells that serve as a platform for multiple signalling molecules and compartmentalise them for optimal function. Caveolae can be seen on a variety of cells, including SMC, epithelial cells, and fibroblasts, in addition to EC. Caveolin-1, a significant protein component of caveolae, maintains caveolae's shape and interacts with a variety of signalling molecules found in or recruited to caveolae, stabilising and keeping them in an inhibitory conformation. Endothelial caveolin-1 has been demonstrated to interact with a vast number of signalling pathways implicated in PH. Endothelium dysfunction, including the loss of functioning endothelial caveolin-1, may be the initial component in the

pathogenesis of PH, as well as contributing to the disease's progression, as a result of injury such as inflammation, toxicity, increased shear stress, and hypoxia.

Conclusion

PAH progresses due to endothelium damage caused by increasing pulmonary flow or pressure. If the vascular alterations are minor, reducing the flow or pressure using a pulmonary artery band results in disease reversal. It is not possible to reverse significant late alterations. The dual function of cav-1 is critical in the course of the disease. The disease is initiated and progressed by the loss of endothelial cav-1 and the reciprocal stimulation of proliferative and anti-apoptotic pathways. Endothelial cav-1 loss and EC disruption are followed by increased expression of cav-1 in SMC and the development of neointima.

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