Pulmonary capillary hemangiomatosis: a focus on the EIF2AK4 mutation in onset and pathogenesis

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Abstract: Pulmonary capillary hemangiomatosis (PCH) is a pulmonary vascular disease that mainly affects small capillaries in the lung, and is often misdiagnosed as pulmonary arterial hypertension or pulmonary veno-occlusive disease due to similarities in their clinical presentations, prognosis, and management. In patients who are symptomatic, there is a high mortality rate with median survival of 3 years after diagnosis. Both idiopathic and familial PCH cases are being reported, indicating there is genetic component in disease etiology. Mutations in the eukaryotic translation initiation factor 2α kinase 4 (EIF2AK4) gene were identified in familial and idiopathic PCH cases, suggesting EIF2AK4 is a genetic risk factor for PCH. EIF2AK4 mutations were identified in 100% (6/6) of autosomal recessively inherited familial PCH and 20% (2/10) of sporadic PCH cases. EIF2AK4 is a member of serine/threonine kinases. It downregulates protein synthesis in response to a variety of cellular stress such as hypoxia, viral infection, and amino acid deprivation. Bone morphogenetic protein receptor 2 (BMPR2) is a major genetic risk factor in pulmonary arterial hypertension and EIF2AK4 potentially connects with BMPR2 to cause PCH. L-Arginine is substrate of nitric oxide synthase, and L-arginine is depleted during the production of nitric oxide, which may activate EIF2AK4 to inhibit protein synthesis and negatively regulate vasculogenesis. Mammalian target of rapamycin and EIF2α kinase are two major pathways for translational regulation. Mutant EIF2AK4 could promote proliferation of small pulmonary arteries by crosstalk with mammalian targets of the rapamycin signaling pathway. EIF2AK4 may regulate angiogenesis by modulating the immune system in PCH pathogenesis. The mechanisms of abnormal capillary angiogenesis are suggested to be similar to that of tumor vascularization. Specific therapies were developed according to pathogenesis and are proved to be effective in reported cases. Targeting the EIF2AK4 pathway may provide a novel therapy for PCH.

Keywords: EIF2AK4, genetics, pulmonary arterial hypertension, pulmonary veno-occlusive disease

Introduction
Pulmonary capillary hemangiomatosis (PCH) is a devastating disease characterized by dysregulated pulmonary capillary angiogenesis infiltrating peribronchial, perivascular interstitium, and lung parenchyma. According to the Fifth World Symposium on Pulmonary Hypertension held in Nice, PCH, together with pulmonary veno-occlusive disease (PVOD), is classified as a subcategory of group 1 pulmonary arterial hypertension (PAH).1

PCH was first described in 1978. The case was characterized by invasive abnormal angiomatous growth in pulmonary intralobular fibrous septa that destroyed and
obstructed pulmonary veins and venules. The disease has been recognized since then, and several cases have been reported. Frequent clinical presentations are dyspnea, hemoptysis, fever, pleural effusions, and crackles on lung auscultation. Chest X-ray, computerized tomography scan of chest, pulmonary function tests, and pulmonary angiography are performed in patients when PCH is suspected. Define diagnosis is made by biopsy, autopsy, or examination of lung explants. In a small number of reported cases, histopathological features of PCH overlapped with PAH and PVOD, as well as some other diseases, such as pulmonary fibrosis, pulmonary embolism, pulmonary hemosiderosis, arteriovenous malformation, lymphangioleiomyomatosis. The characters of primary PAH, PVOD, and PCH cases are listed in Table 1 for comparison. Symptomatic PCH cases are rare occurrences, with approximately only 100 cases reported before 2011.

The etiology of PCH is currently unknown. It is proposed that PCH is an angiogenic disease. Angiogenic factors such as platelet-derived growth factor, vascular endothelial growth factor, and angiopoietin are increased in PCH, which are responsible for the pathological growth of capillary blood vessels, while angiogenic factors are usually tightly regulated so that neovascularization is not occurring in the normal situation. On the contrary, histopathology examination indicated that endothelial cells that comprise PCH lesions are cytologically bland and show no mitotic activity. PCH usually occurs diffusely in both lungs with or without PAH development. In some instances, solitary nodules or focal PCH-like lesions have been found in lung periphery in patients who had no clinical symptoms of the disease. This constitutes 5.7% of autopsies examined. In these cases, subjects are male dominant (nine males and one female) with an average age of 65 years, indicating that there is a different etiology for this subgroup of patients. It has been reported that PCH can occur in association with cardiomyopathy, aortic stenosis, Kartagener syndrome, congenital diaphragmatic hernia, connective tissue diseases such as systemic lupus erythematosus, and scleroderma. Takayasu’s arteritis, and cancer. Recurrence of PCH after bilateral lung transplantation was reported, suggesting that there is an infectious or inflammatory cause inciting uncontrolled angiogenesis. The etiology of PCH may be genetic: both sporadic and familial PCH cases have been observed. Most familial PCH cases are autosomal recessively inherited, but autosomal dominant inheritance has also been reported.

### EIF2AK4 as a novel genetic cause of PCH

Eukaryotic translation initiation factor 2α kinase 4 (EIF2AK4) is presented in all eukaryotes from yeast to mammals and plays an important role in the transcriptional regulation. Using whole exome sequencing, novel mutations in EIF2AK4 gene were identified in familial PCH case patients. In one family, both affected brothers had compound heterozygous mutations, c.1153dupG (p.Val385fs) and c.3766C>T (p.Arg1256X), in EIF2AK4. Unaffected parents were heterozygous carriers of one of the two mutations (the mother carried the frameshift mutation, c.1153dupG, and the father carried the nonsense mutation, c.3766C>T). Ten additional sporadic PCH case patients were screened for EIF2AK4 mutations by Sanger sequencing. A homozygous frameshift mutation c.1392delT (p.Arg465fs) was found in one subject. Another patient had a compound heterozygous splice mutation (c.860-1G>A) and a nonsense mutation, c.3438C>T (p.Arg1146X). No mutations were identified in this gene in one autosomal-dominant familial PCH case. All subjects recruited in the study were histologically confirmed to have PCH. There are a total of five mutations identified in EIF2AK4 gene in PCH patients. Mutations occurred in one autosomal recessively inherited familial PCH case but no mutation was found in an autosomal dominantly inherited familial PCH case. EIF2AK4 mutations occurred in 20% (2/10) sporadic PCH cases. Patients who have the same mutations in EIF2AK4 had different age of onset and different severity of the disease. This suggests that additional genetic and/or environmental factors may modify the onset and severity of PCH in association with EIF2AK4 mutations.

EIF2AK4 is a member of serine/threonine kinases that downregulates protein synthesis in response to a variety of cellular stress and amino acid deprivation. EIF2AK4, also called general control nondepressible-2 (GCN2), is activated by amino acid deprivation, viral infection, proteasome inhibition, and hypoxia. EIF2AK4 has 1,649 amino acids, encoding RWD (RING finger-containing proteins, WD-repeat-containing proteins, and yeast DEAD [DExD]-like helicases) domain, pseudokinase domain, protein kinase domain, and histidyl-t-RNA synthetase (HisRS)-related domain. Expression of EIF2AK4 can be found in all human tissues, including lung and aorta endothelial cells. Immunohistochemistry indicated that EIF2AK4 is expressed in smooth muscle cells in small pulmonary venules. There is a diffuse interstitial staining. Macrophages and some mononuclear cells are positive for staining but endothelial cells are negative for EIF2AK4 in pulmonary veins. EIF2AK4 expression was not detected in PVOD mutant lungs. In PCH
Table 1 Comparison of PAH, PVOD, and PCH

<table>
<thead>
<tr>
<th></th>
<th>PAH</th>
<th>PVOD</th>
<th>PCH</th>
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<tr>
<td><strong>Epidemiology</strong></td>
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<tr>
<td>Incidence</td>
<td>2–5 per million.</td>
<td>Subgroup of PAH. 0.1–0.2 cases per million in general population represents 5%–10% of cases where patients were initially diagnosed as IPAH.</td>
<td>Subgroup of PAH, with only approximately 100 cases reported until 2011.</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>All age groups.</td>
<td>All age groups but affecting mostly children and young adults</td>
<td>All age groups but mean age at diagnosis 28.8 yearsFemale:male = 1:1</td>
</tr>
<tr>
<td>Sex</td>
<td>Female:male = 1:1.</td>
<td></td>
<td></td>
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<tr>
<td><strong>Risk factors</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Tobacco</td>
<td>Unrelated.</td>
<td>Tobacco exposure is significantly higher than PAH patients.</td>
<td>Unknown.</td>
</tr>
<tr>
<td>Anorexigen</td>
<td>Anorexigen use was reported significantly more frequently in PAH than PVOD patients.</td>
<td></td>
<td>Not reported.</td>
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<td><strong>Clinical characteristics</strong></td>
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<tr>
<td>Clinical presentations</td>
<td>Progressive dyspnea on exertion, syncopy, hemoptysis, clubbing, and right heart failure.</td>
<td>Progressive dyspnea on exertion, hemoptysis, prominent second heart sound, crackles on lung auscultation and right heart failure.</td>
<td>Dyspnea, hemoptysis, fever, pleural effusions, cyanosis, chest pain, crackles on lung auscultation, epistaxis, clubbing, right heart failure.</td>
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<td>NYHA functional class</td>
<td>Class I, II, III, or IV.</td>
<td>Most of the PVOD patients have functional class of III or IV at the time of diagnosis.</td>
<td>Symptomatic PCH patients often have functional class of III or IV at the time of diagnosis.</td>
</tr>
<tr>
<td>at the time of diagnosis</td>
<td></td>
<td>PVOD patients have lower right atrial pressure than PAH group.</td>
<td>No difference between PCH and PVOD patients who have EIF2AK4 mutations.</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>Mean pulmonary arterial pressure $&gt; 25$ mmHg and pulmonary capillary wedge pressure $= 15$ mmHg.</td>
<td>PVOD patients have lower PaO$_2$ (at rest), DLCO, DLCO/VA when compared with PAH patients.</td>
<td>No difference between PCH and PVOD patients who have EIF2AK4 mutations.</td>
</tr>
<tr>
<td>Pulmonary function</td>
<td>Normal (possible mild restrictive pattern) with often reduced PaO$_2$ (at rest), DLCO and DLCO/VA.</td>
<td>Not associated with better prognosis because of pulmonary edema when treat with vasodilators.</td>
<td>Not associated with better prognosis because of pulmonary edema when treat with vasodilators.</td>
</tr>
<tr>
<td>tests</td>
<td></td>
<td></td>
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<tr>
<td>NO response</td>
<td>Associated with CCB response and better prognosis.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>CXR, EKG, echo, and pulmonary function test.</td>
<td>After diagnosis of PAH, integrated results of high resolution CT (septal lines, ground glass opacities, and lymph node enlargement), pulmonary function test (lower diffusing capacity of lung for carbon monoxide), bronchoalveolar lavage (occult alveolar hemorrhage), and arterial blood gas (lower PaO$_2$ at rest) suggest PVOD. Definite diagnosis is made by surgical biopsy but is associated with high risk and is not recommended.</td>
<td>After diagnosis of PAH, integrated results of high resolution CT (septal lines, ground glass opacities, and lymph node enlargement), pulmonary function test (lower diffusing capacity of lung for carbon monoxide), bronchoalveolar lavage (occult alveolar hemorrhage), and arterial blood gas (lower PaO$_2$ at rest) suggest PVOD. Definite diagnosis is made by surgical biopsy but is associated with high risk and is not recommended.</td>
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<td>Pathology</td>
<td>Obstruction, proliferation, and remodeling of small precapillary pulmonary arteries characterized by smooth muscle proliferation, medial hypertrophy, intimal fibrosis, in situ thrombosis, and plexiform lesions.</td>
<td>Dilatation and proliferation of postcapillary venous pulmonary vessels characterized by intimal fibrosis in septal veins and preseptal venules, occult alveolar hemorrhage in bronchoalveolar lavage, doubling or tripling of the alveolar septal capillary layers, and in situ thrombosis. Lymphatic involvement is frequently observed.</td>
<td>Uncontrolled proliferation of pulmonary capillaries infiltrating vascular, bronchial and interstitial pulmonary structures.</td>
</tr>
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<td>Genetics</td>
<td>Familial or sporadic cases. There is genetic heterogeneity. BMPR2 mutations were found in 70% of hereditary PAH and 10%–40% of idiopathic PAH. The penetrance is 20%. ALK1, ENG, SMAD4, SMAD9, CAV1, and KCNK3 are rare genetic causes of PAH. TBX4 mutations were detected in 30% pediatric PAH.</td>
<td>Familial or sporadic cases. There are six BMPR2 mutations found in PVOD cases. EIF2AK4 mutations were identified in 13/13 of autosomal recessive familial and 5/20 sporadic PVOD cases.</td>
<td>Familial or sporadic cases. EIF2AK4 mutations were identified in seven autosomal recessively inherited PCH and 2/12 sporadic PCH cases. EIF2AK4 mutation was not found in one autosomal dominantly inherited PCH case.</td>
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patients, how EIF2AK4 regulates pulmonary angiogenesis and whether EIF2AK4 mutations identified in these patients are gain- or loss-of-function are not clear at this point.

**EIF2AK4 and bone morphogenetic protein**

Why EIF2AK4 mutation could cause abnormal angiogenesis in lungs in PCH patients remains unknown. **EIF2AK4**-knockout mice were generated. Mutant mice are viable, fertile, and exhibit no phenotypic abnormalities under standard growth conditions. The lungs of these mutant mice have not been examined. In coping with stress, EIF2AK4 decreases global protein synthesis, increasing specific mRNA synthesis for transcription factors and enabling cells to initiate a survival response to the initial activating cue. **EIF2AK4** may regulate bone morphogenetic protein receptor 2 (BMPR2)-transforming growth factor-beta pathway, which is known to be the genetic cause of PAH. It is reported that EIF2AK4 binds with mothers against decapentaplegic drosophila homolog of 4 (SMAD family member 4) and transforming growth factor-beta receptor 1 in human embryonic kidney cells to regulate the epithelial–mesenchymal transition. **EIF2AK4** regulates activating transcription factor 4 (ATF4), which transcriptionally regulates the Tribbles homolog 3. In human primary pulmonary artery smooth muscle cells, Tribbles-like protein 3 interacts with BMPR2 on the cell surface through BMPR2 tail domain. Further studies are needed to investigate whether EIF2AK4 interplays with bone morphogenetic protein signaling in pulmonary blood vessels and if mutations in EIF2AK4 could cause BMPR2 haplinsufficiency in PCH.

**EIF2AK4 and nitric oxide synthase**

EIF2AK4 is activated by amino acid depletion. 1-arginine is a substrate of nitric oxide synthase (NOS), and 1-arginine will be depleted during the production of nitric oxide. Study indicated that the depletion of 1-arginine will activate EIF2AK4. **EIF2AK4** will downregulate protein synthesis on activation. In mouse skin, NOS mediates ultraviolet light-induced **EIF2AK4**-arginine starvation signaling pathways. In human, there are three types of NOSs, including neuronal, inducible, and endothelial NOS. Endothelial NOS (eNOS) is expressed in pulmonary vascular endothelium and is involved in PAH pathogenesis. An animal study indicated that there are microvascular endothelial progenitor cells in pulmonary arteries. These cells express eNOS and possess vasculogenic capacity while maintaining functional endothelial microvascular specificity. It is possible that
EIF2AK4 activation can be induced by L-arginine depletion due to eNOS activity, and EIF2AK4 prevents abnormal vasculogenesis. It will be informative to investigate if EIF2AK4 inactivation could affect homeostasis of angiogenesis through eNOS in PCH lungs.

**EIF2AK4 and mammalian target of rapamycin**

Target of rapamycin (TOR) and EIF2α kinase are the two major pathways for translational regulation. These two signal transduction pathways react to amino acid deprivation by inhibiting general protein translation, while at the same time, increasing translation of specific mRNAs involved in restoring homeostasis. EIF2AK4 senses the absence of one or more amino acids by virtue of direct binding to the uncharged tRNAs. The presence of certain amino acids, such as leucine, permits activation of the master growth regulating kinase TOR. Studies from yeast and mammals indicate that EIF2AK4 and TOR pathways are interlinked, and the crosstalk between the two pathways varies with the actual stress applied. Mammalian TOR (mTOR) is a downstream effector of the phosphatidylinositol 3-kinase/Akt, and mTOR regulates ribosomal p70 S6 kinase (S6K1) and the mRNA cap-binding protein inhibitory protein, 4E-BP1 in response to stimuli. EIF2AK4 contributes to the regulation of 4E-BP1 and S6K1 in response to leucine depletion in EIF2AK4-knockout mice. Evidence suggested the critical role of mTOR in remodeling small pulmonary arteries and PAH. mTOR increases proliferation and cell survival in chronic hypoxia, and the inhibition of mTOR activity may provide a novel treatment for PAH patients. It is possible that the loss of EIF2AK4 could promote proliferation of small pulmonary arteries by crosstalk with mTOR signaling pathway.

**EIF2AK4 and immune system**

Macrophages and neutrophils are involved in angiogenesis in lung tumor formation. Studies indicated that increased inflammation, such as pulmonary infiltration of macrophages, is one of the pathologic phenotypes in PAH. EIF2AK4 expression was observed in macrophages and in some mononuclear cells in lungs. This suggested that EIF2AK4 may regulate angiogenesis by modulating the immune system in PCH pathogenesis. Mutations in EIF2AK4 may inactivate macrophages and reduce cytokine production and immune response. This is proved by an animal study. A recessive loss-of-function mutation in EIF2AK4 mutant mouse strain was isolated by screening macrophage’s susceptibility to virus infection. EIF2AK4 mutant mice showed innate immune defect and modest increase in susceptibility to DNA viruses’ mouse cytomegalovirus infection. Furthermore, macrophage is one of the immune cell types that produces α-interferon, and interferon-2α has been applied in PCH treatment successfully.

**EIF2AK4 and tumor**

In response to stress, EIF2AK4 induces phosphorylation of the alpha (α) subunit of the translation initiation factor eIF2 at serine 51 (eIF2αS51P), and the latter plays an essential role in stress-induced tumorigenesis. Evidence suggested that EIF2AK4-eIF2α-ATF4 pathway regulates mitochondrial phosphoenolpyruvate carboxykinase (PEPCK-M), which is presented in tumor of several origins and played an important role in cancer metabolism. EIF2AK4-eIF2alpha-ATF4 pathway is critical for maintaining metabolic homeostasis (such as oxygen and nutrient) in tumor cells and is a potential target for tumor therapy. In human tumors, EIF2AK4/ATF4 regulates tumor growth and angiogenesis through amino acid deficiency-mediated vascular endothelial growth factor. It is possible that EIF2AK4 regulates vascular growth in PCH through similar mechanisms observed in tumor.

**Correlate PCH case pathogenesis with diagnosis and treat**

EIF2AK4 mutations were found in some subjects in both PCH and PVOD groups, indicating that these two diseases could not be differentiated by genetic testing. Clinical data were collected from previously reported PCH case and PVOD patients who carried EIF2AK4 mutations. Clinical features of patients who had mutations in EIF2AK4 in PCH cases and PVOD were compared. Results indicated that there is male predominance (three males and one female) in PCH cases when compared with PVOD (13 males and 13 females) but the difference is not statistically significant (Table 2). This indicated that the pathogenesis of PCH and PVOD might be distinct. There is no difference in other characters including age at diagnosis, mean pulmonary arterial pressure, pulmonary capillary wedge pressure, diffusing capacity of the lung for carbon monoxide (DLCO), and ratio of number of patients who had lung transplantation versus no lung transplantation between these two groups (Table 2). When pulmonary function variables were compared between PAH and EIF2AK4 mutant PVOD patients, significantly reduced DLCO and increased ventilator demand to cardiopulmonary exercise testing in PVOD group were observed. These studies are helpful for the identification of disease mechanisms and genotype phenotype correlations.
been identified in 70% of heritable PAH and 10%–40% of idiopathic PAH. Six BMPR2 mutations were reported in PVOD patients. However, no BMPR2 mutations were found in PCH patients.

Treatments used for other causes of pulmonary hypertension, such as diuretics, corticosteroids, and warfarin, are also used to treat PCH. However, these drugs are relatively ineffective, and the prognosis is poor. This is probably because pathogenesis of PAH is arteriolarization of small pulmonary arteries, while PCH develops due to abnormal angiogenesis which occludes pulmonary veins and venules. It is also possible that PAH and PCH have different etiologies. Vasodilators such as prostacyclin therapy, a mainstay in the treatment of pulmonary hypertension, have been reported to cause sudden respiratory distress or death and have to be used cautiously in PCH patients. Platelet-derived growth factor and its receptor have been implicated in the pathogenesis of PCH. Imatinib, a platelet growth factor receptor antagonist, showed efficacy in PCH treatment. Doxycycline, a matrix metalloproteinase and angiogenesis inhibitor, could be a treatment option for the PCH patients who have elevated levels of matrix metalloproteinase and capillary proliferation. Interferons are cytokines secreted by host cells in response to stimuli. Interferons can inhibit proliferation and collagen synthesis, inhibit cell motility, enhance prostacyclin production, enhance phagocytic activity of macrophages, and modulate immune system. There are three main types of interferons known as alpha, beta, and gamma. Interferon alpha-2a has been used in the treatment of PCH and is effective in a few cases.

Targeting EIF2AK4-ATF4 pathway may provide a novel therapy for PCH patients. For medication nonresponders, lung transplantation is considered as definitive treatment.

**Table 2** Comparison of clinical characteristics in PCH and PVOD patients with EIF2AK4 mutations

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PCH (n=4)</th>
<th>PVOD (n=26)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (range)</td>
<td>20.5 (15, 33)</td>
<td>24.5 (11, 50)</td>
<td>0.39</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>3 (75%)</td>
<td>13 (50%)</td>
<td>0.60</td>
</tr>
<tr>
<td>mPAP, median (range)</td>
<td>52 (40, 77)</td>
<td>50.5 (22, 75)</td>
<td>0.58</td>
</tr>
<tr>
<td>PCWP, median (range)</td>
<td>6.5 (3, 15)</td>
<td>6.5 (3, 15)</td>
<td>1</td>
</tr>
<tr>
<td>DLCO, median (range)</td>
<td>31 (26, 33)</td>
<td>32 (18, 65)</td>
<td>0.96</td>
</tr>
<tr>
<td>Lung transplantation, yes (%)</td>
<td>3 (75%)</td>
<td>18 (69.2%)</td>
<td>1</td>
</tr>
</tbody>
</table>

**Notes:** R software (version 3.1.2) was used for statistical analysis. Comparisons of sex and lung transplantation variables were assessed by Fisher’s exact test, and comparisons of all of the other variables were assessed by Wilcoxon signed-rank test. P-values are for two-tailed tests. A P-value <0.05 was considered to be statistically significant.

**Abbreviations:** PCH, pulmonary capillary hemangiomatosis; PVOD, pulmonary veno-occlusive disease; EIF2AK4, eukaryotic translation initiation factor 2-alpha kinase 4; mPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; DLCO, diffusing lung capacity of carbon monoxide.

**Conclusion**

PCH is a subgroup of PAH characterized by uncontrolled capillary proliferation in the lung. Clinically, PCH can be asymptomatic, develop with or without PAH, or develop in association with other diseases. This indicated that the disease is heterogeneous. Mutations in EIF2AK4 were found in one autosomal recessively inherited PCH case and 20% (2/10) idiopathic PCH case, suggesting that EIF2AK4 is a genetic risk factor for a subgroup of PCH patients. EIF2AK4 encodes a protein kinase that downregulates the protein synthesis in response to varied cellular stress. EIF2AK4 may interact with BMPR2, NOS, and mTOR to regulate angiogenesis. Evidence also suggested EIF2AK4 can regulate immune system in response to infection or regulate angiogenesis through similar mechanisms observed in tumor. Medications used for PAH were applied in PCH treatment but are relatively ineffective. Vasodilators should be used cautiously due to risk of pulmonary edema, respiratory distress, and death. Medications targeting pathogenesis of PCH, such as imatinib, doxycycline, and interferon alpha-2a, are reported to be effective in some cases. Targeting EIF2AK4 pathway could provide a potential novel therapy for PCH. EIF2AK4 mutations were identified in a small portion of sporadic PCH cases, and no mutations were found in autosomal dominantly inherited PCH cases, indicating that there are other genetic factors associated with PCH.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**

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