Review

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Interleukin-13 in the pathogenesis of pulmonary artery hypertension

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Abstract

Background: Interleukin (IL)-13 is a regulatory factor of tissue remodeling and is involved in the pathogenesis of pulmonary artery hypertension (PAH). However, the implications of IL-13 in PAH remains uncertain. This article aims to describe the current knowledge on production and function of IL-13 and its receptors in the mechanisms of PAH.

Content: The study materials of this article were based on comprehensive literature retrieval of publications of IL-13 in PAH. These study materials were carefully reviewed, analyzed and discussed.

Summary: IL-13 levels in blood and lung tissue were elevated in both animal models of PAH and patients with PAH in comparison to non-PAH controls. Types I and II IL-13 receptors participate in pulmonary artery remodeling through signal transducer and activator of transcription (STAT)6 or through phosphatidylinositol 3-kinase (PI3K), STAT3 and mitogen activated protein kinase (MAPK) pathways. Oxidant, arginase 2 (Arg2) and hypoxia-inducible factor 1 α are involved in the proliferation of pulmonary artery smooth muscle cells.

Outlook: Types I and II IL-13 receptors play an important role in the IL-13 signaling by STAT6 via Janus kinase kinases, and by PI3K, STAT3 and MAPK pathways, respectively. Alternative pathways, including oxidant, Arg2 and hypoxia-inducible factor 1 α might be also involved in the pathological process of PAH development. Investigational therapies by inflammatory suppression or thrombolytic and anticoagulant agents could inhibit intimal hyperplasia of the pulmonary arteries and suppress pulmonary vasculature remodeling. Drug research and development oriented by this hypothesis would confer benefits to the treatment of PAH.

Keywords: interleukin-13; interleukin-13 receptors; pulmonary hypertension; signal transduction.

Introduction

Pulmonary artery hypertension (PAH) is diagnosed as an elevation of mean pulmonary artery pressure to >25 mm Hg at rest or to >30 mm Hg during exercise. The major pathological changes of PAH are pulmonary arterial remodeling, leading to severe hypoxia and elevation of pulmonary vascular resistance [1]. In neonates, PAH may eventually lead to life-threatening circulatory failure [2, 3].

It has been recognized that the interleukin (IL) family members are involved in the etiologies of various inflammation-related conditions, such as infectious diseases [4–6], immunological disorders [7–10] and neoplasms [10]. In a comprehensive review article that depicted IL-6 profiles in patients receiving different cardiac operations. It was reported that IL-6 and other cytokine levels were much higher in patients with PAH than in those without, and that patients undergoing pulmonary endarterectomy under profound hypothermic circulatory arrest were associated with significantly elevated IL-6 levels [11]. It was therefore proposed that, in these conditions, elevation of IL-6 was probably the results of the inflammatory process in relation to anesthesia, surgical trauma, cardiopulmonary bypass and perioperative complications. Besides, mutations, environmental changes and acquired adjustment of transforming growth factor (TGF)- β superfamily-related genes may explain at least partly the mechanisms of congenital PAH [12–14]. In these studies, it was revealed that an imbalance of vascular cellular proliferation, driven by stimulation of excessive growth factors, such as TGF- β family signaling, platelet derived growth factor (PDGF) and Notch receptor play an important role in the development of PAH [15]. It has been noted that, in the developmental course of PAH, the immune cells initiate and maintain inflammatory responses to infections [16, 17], and to hypoxic insults of the lung [18, 19]. All these pathological processes have an inextricable relationship with ILs [20, 21]. Recent studies suggested that IL-13, a T helper

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type 2 (Th2) cell effector cytokine, should be involved in the mechanism of PAH; however, there is no direct evidence to prove it. In this article, the current knowledge on production and function of IL-13 and its receptors in the mechanisms of PAH are described.

IL-13 and its receptors

IL-13

IL-13 is a 33-amino acid peptide cytokine, its gene is located on chromosome 5q31, and the transcription of IL-13 is regulated by *GATA3* [22, 23]. In humans, various innate immune cells including eosinophils, basophils, mast cells, natural killer cells and natural killer T cells produce IL-13 [24].

IL-13 regulates inflammation, mucus production, tissue remodeling and fibrosis. IL-13 may affect cells of various structures, especially promoting epithelial cell differentiation and may amplify with IL-4 the Th2 response and immunoglobulin E synthesis [25]. IL-13 is regarded as independent and cross-inhibitory inducer of inflammation and tissue destruction/remodeling, IL-13- and IL-17A-coinduced inflammation are involved in the development of PAH [26]. IL-13-activated monocyte/macrophages may play an important role in the development of PAH, in which c-type mannose receptor 1 (MRC1) was highly induced by IL-4/IL-13 in human monocytes in relation to PAH and mortality of PAH [27]. Daley et al. [28] have shown the relations between pulmonary arterial muscularization and IL-13: depletion of CD4⁺ T cells, antigen-specific Th2 response, or the pathogenic IL-13 expressions significantly ameliorated pulmonary arterial muscularization. IL-13 can mediate pulmonary arterial muscularization via a cooperative mechanism between IL-13 and components of the immune and inflammatory responses [28].

Clinical observations revealed that both IL-13 and IL-4 regulate the responses of lymphocytes, and myeloid and non-hematopoietic cells, and regulate allergic inflammation [29]. It was also reported that circulating IL-13 levels were elevated in patients with systemic sclerosis-associated PAH [30] and schistosomiasis-associated PAH [31], in comparison to non-PAH controls, IL-13 was also upregulated in lung tissue from patients with idiopathic pulmonary fibrosis [32]. However, Hecker et al. [33] described somewhat contradictory results of IL-13 signaling in that it suppresses proliferation of human pulmonary artery smooth muscle cell (paSMCs) *in vitro*. Ferreira et al. [31]

determined serum levels of TGF- β_1 and IL-13 by enzyme-linked immunosorbent assay (ELISA), and noted that PAH patients with significant higher TGF- β_1 than non-PAH patients (22496.9 pg/mL vs. 13629.9 pg/mL, $p=0.006$), but no intergroup difference was found in IL-13. There was no difference in the median value of in the group with schistosomiasis-associated PAH compared to those without (152.3 pg/mL vs. 131.8 pg/mL, $p=0.177$). Zorzaneli et al. [34] disclosed that IL-13 was closely related to the age of the pediatric patients with PAH ($r=0.33$, $p=0.022$). In addition, in an established pulmonary vascular remodeling and PAH mouse model induced by *Schistosoma mansoni*, Crosby et al. [35] found the degree of vascular remodeling correlated with proximity to granulomas. The elevation of right ventricular systolic pressure and right ventricular hypertrophy at 25 weeks relied on the presence of the eggs in the lung.

IL-13 receptors

Unlike IL-4, which signals via either the type I (IL-4R α / γ c) or the type II (IL-4R α /IL-13R α_1) IL-4 receptor, IL-13 signals only through the type II IL-4 receptor, and it binds to two cell surface receptors: IL-13R α_1 and IL-13R α_2 . The IL-13-IL-13R α_1 -IL-4R α complex functions to activate Janus kinase (Jak)2, and Jak1 kinases and signal transducer and activator of transcription (Stat)6. Jak3 is associated with γ c and is crucial for signaling via the type I other than the type II IL-4 receptor [36]. The IL-13R α_1 receptor binds IL-13 with low affinity, and forms the type I IL-13 receptor, i.e. IL-13R α_1 /IL-4R α heterodimer, by dimerizing with IL-4R α . The type I IL-13 receptor signals primarily through phosphorylation of STAT6 via Jak kinases, or through intracellular signaling pathways, such as phosphatidylinositol 3-kinase (PI3K), STAT3 and mitogen activated protein kinase (MAPK) [37]. In contrast, the type II IL-13 receptor binds only IL-13, forming IL-13R α_2 monomer, with higher affinity than the type I IL-13R α_1 /IL-4R α receptor, and usually does not have signaling in spite of reported MAPK, PI3K and STAT3 activation. This affinity provides IL-13R α_2 with time and space to capture, deactivate and even scavenge IL-13 [33]. The co-expressions of the two receptors predispose to inhibit the production of phosphorylated STAT6 induced by IL-13 [38], which is ascribed to the preferential binding between IL-13 and IL-13R α_2 . In the absence of IL-13, IL-13R α_2 inhibits IL-4 induced phosphorylated STAT6 by interacting with IL-4R α [39]. This phenomenon supports that IL-13R α_2 could regulate the inhibition of type I receptor signaling by alternative

pathways other than IL-13 scavenging. IL-13R α 2 expression can be induced in lung fibroblasts by IL-4 or IL-13 via a STAT6-dependent mechanism, or by tumor necrosis factor- α via a STAT6-independent mechanism. Endogenous IL-13R α 2 decreases binding affinity to IL-13 in lung fibroblasts but does not influence the binding to IL-4. As a result, endogenous IL-13R α 2 does not activate any unique IL-13-mediated gene expressions [32].

Experimental studies revealed that IL-13R α 2 might contribute to allergic inflammation as it was observed that IL-13R α 2-deficient mice showed attenuated airway inflammation in comparison to wild-type mice after HDM challenge [40]. IL-13R α 1/IL-13R α 2 balance regulates IL-13-mediated responses and implicates smooth muscle hypertrophy associated with pathological vascular remodeling in PAH [33]. Graham et al. [41] demonstrated that mice with loss of IL-13R α 1 function did not develop PAH with reduced pulmonary vascular remodeling, while gain-of-function IL-13R α 2 $^{-/-}$ mice developed PAH with exacerbated vascular remodeling. They also observed that expression of a target of IL-13 signaling resistin-like molecule- α was upregulated in infected wild-type and IL-13R α 2 $^{-/-}$ mice but not in IL-13R α 1 $^{-/-}$ mice, indicating that the development of PAH relied on upregulated IL-13 signaling [41]. It was observed in patients with idiopathic PAH and in PAH animal models, that the upregulated IL-13R α 2 in lung tissue in comparison to IL-13R α 1 could be a key feature of IL-13 signaling in PAH [33]. IL-13 suppresses proliferation of paSMC by promoting G $_0$ /G $_1$ arrest, and IL-13 suppresses endothelin-1 production by paSMC [33]. Increased IL-4 and IL-13 mRNA and protein levels were observed in experimental PAH models, implying that IL-4/IL-13 and TGF- β interact mutually [42]. Hecker et al. [33] found that the expression of IL-13R α 2 in the lung tissue was upregulated in patients with idiopathic PAH and in animal models of idiopathic PAH.

The transcription and production of IL-13 are enhanced by GATA3 but suppressed by interferons [43]. The IL-13 signal transduction through the Jak/STAT pathway can induce the inhibition of cytokine signaling protein, which in fact weakens the IL-13 signal itself [44]. The IL-13R α 2 receptor can be a negative regulator of IL-13 as it regulates IL-13 expression by impacting on IL-13-induced STAT6 activation [45]. Soluble IL-13R α 2 produced by alternative splicing is more active and is with greater binding affinity to IL-13. It serves as an inhibitory protein to regulate IL-13 responses [46]. IL-13R α 2 receptor and the Jak/STAT pathway may therefore suppress the allergic and inflammatory reactions by dysregulating GATA3 and by enhancing interferons. The IL-13 signaling is shown in Figure 1.

Figure 1: Interleukin-13 signaling pathway in development of pulmonary artery hypertension.

IL, interleukin; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; PA, pulmonary artery; PAH, pulmonary artery hypertension; PI3K, phosphoinositide 3-kinase; R, receptor; STAT, signal transducer and activator of transcription.

Oxidant signaling

It was reported that PDGF promotes the expression of IL-13 in lung smooth muscle cells through an oxidant signaling, and treatment of cultured human airway or paSMCs with PDGF promotes IL-13 mRNA and protein expression, and PDGF-induced IL-13 expression could be suppressed by the inhibition of reactive oxygen species signaling [47]. In other words, PDGF promoted IL-13 expressions in lung SMCs, which could be inhibited by reactive oxygen species [47].

IL-13R α 2-arginase 2 (Arg2)-dependent pathway

IL-13 may contribute to development of PAH via an IL-13R α 2-arginase 2 (Arg2)-dependent pathway. Cho et al. [27] investigated pulmonary vascular remodeling in lung-specific IL-13 overexpressing transgenic mice. They observed that IL-13 transgenic mice spontaneously developed PAH phenotype at 2 months of age, and also showed increased activity of Arg2 in IL-13 transgenic lungs. It was interpreted that Arg2 could decrease bioavailability of nitric oxide in the pulmonary vasculature by competing

with nitric oxide synthase 3 for the substrate L-arginine. When IL-13 transgenic mice were crossed with Arg2^{-/-} mutant mice, pulmonary vascular remodeling and right ventricular systolic pressure were remarkably attenuated, and the production of nitric oxide was increased in the lung tissue. When treated with recombinant IL-13, human paSMC proliferation was observed in an Arg2-dependent manner. The proliferation of human paSMC by Arg2 was markedly decreased with the elimination of the *IL-13Rα2* gene in human paSMC. The IL-13 regulated cellular proliferation and Arg2 expression in human paSMC were remarkably reduced with IL-13Rα2 siRNA silencing [27].

Hypoxia-inducible factor 1α (HIF-1α) pathway

IL-13 increased the expression and activity of HIF1α via IL-13Rα2, as well, and that IL-13-induced proliferation of human paSMC was significantly decreased with *HIF1α* gene knockdown. Moreover, HIF1α might regulate Arg2 expression at the transcriptional level. These findings implicated the important role of HIF1α in IL-13-induced proliferation of paSMCs [27].

Treatment

The antigen-specific T helper type 2 (Th2) cytokines IL-4, IL-5, and IL-13 are critical for protective immunity against infections and various inflammatory disorders [48, 49]. CD4⁺ T cells, the IL-4-induced Th2 response, and endogenous IL-13 are major requisites leading to allergen- and parasite-associated pulmonary arterial muscularization [28]. Therefore, depletion of CD4⁺ T cells, Th2 response or IL-13 may significantly ameliorate pulmonary arterial remodeling [28].

IL-4 first binds to the IL-4Rα subunit with high affinity followed by dimerization with γc receptor subunit and subsequent JAK-STAT6 activation [50]. Experimental *Schistosomiasis*-associated PAH potentially depends on upregulation of IL-13 [35]. The levels of IL-13, IL-4Rα, phospho-STAT6 and periostin, a target of IL-13 signaling, were increased in the lungs of patients with *Schistosomiasis*-associated PAH and mice with experimental lung disease [51]. In a mouse model of *Schistosoma*-induced PAH, the whole-lung IL-4 and IL-13 levels were significantly increased when the animals were exposed to *Schistosoma*, and an immunohistochemical study revealed a positive staining for IL-4, IL-13 and phospho-STAT6 in the lung

tissues [48]. The gain-of-function IL-13Rα2^{-/-} mice predisposed to exacerbated vascular remodeling and PAH, whereas mice with loss of IL-13Rα1 function had reduced pulmonary vascular remodeling and did not develop PAH [41]. IL-4^{-/-}IL-13^{-/-} mice exposed to *Schistosoma* eggs have decreased right ventricular pressure and vascular remodeling. IL-4/IL-13 can activate TGF-β₁ via phospho-STAT6 signaling, or via increased matrix metalloproteinase-9. Preclinical blockade of STAT6 using a pharmacologic inhibitor resulted in the prevention of the experimental PAH phenotype, novel therapeutic approaches in *Schistosoma*-PAH may thus include targeting both IL-4 and IL-13 cytokines, inhibiting STAT6, and/or blocking TGF-β signaling in the vasculature [51]. Thus, the blockade of TGF-β signaling may also lead to reduced IL-4 and IL-13 levels [42]. Semaxanib (SU5416) is an effective, selective vascular endothelial growth factor receptor (Flk-1/KDR) inhibitor, which acts to downregulate the expressions of both IL-4 and IL-13. Thus, SU5416 could inhibit IL-13 by decreasing adventitial inflammatory reactions [52]. Praziquantel, an anti-worm agent to treat parasite infections, serves to prevent the rise of right ventricular systolic pressure and right ventricular hypertrophy by eliminating the eggs from the feces and eggs from the lung and liver tissues, thereby reversing the established pulmonary vascular remodeling. Moreover, praziquantel can significantly reduce lung expressions of mRNAs of IL-13, IL-8 and IL-4.

Resistin-like molecule (RELM)-α, a striking downstream product of the IL-4 and IL-13 signaling pathways in allergen- and parasite-associated Th2 responses, is overexpressed in the lungs regulated by Th2- and IL-13-mediated inflammation and hypoxia. RELM-α-knockout mice inhibited pulmonary vascular remodeling and the increase of pulmonary pressure and cardiac hypertrophy, thus leading to less vessel muscularization, less perivascular inflammation and reduced medial thickness of intraalveolar vessels [53]. It was observed that the expressions of RELM-α, were increased associated with an enhanced IL-13 signaling in infected wild-type and IL-13Rα2^{-/-} but not IL-13Rα1^{-/-} mice. In a distinct mouse model, Th2-driven inflammation by inhaled *Aspergillus* also led to RELM-α upregulation and vascular remodeling. In addition, *Schistosoma mansoni*-infected mice developed PAH in the absence of IL-13Rα2, suggesting that enhanced IL-13 signaling is sufficient to cause PAH. Generally speaking, the enhanced IL-13 signaling or overexpressed RELM-α but not necessarily IL-13Rα2 or hypoxia are prerequisites of pulmonary vascular remodeling and development of PAH. As a result, the suppression of IL-13 signaling by knocking out IL-13Rα1 led to attenuated pulmonary artery remodeling and PAH, associated with suppression of RELM-α signaling [41].

IL-17A is expressed by fibroblasts, epithelial cells, vascular endothelial cells, B and T cells, myelomonocytic cells, and bone marrow stromal cells. IL-17A and TH17 cells are involved in several inflammatory disorders, IL-17A acts in response to different pathogens by upregulating the expressions of proinflammatory cytokines, chemokines and metalloproteinases. By inducing cells to produce chemokines, IL-17A attracts neutrophils to mediate defenses against [54]. Th17 cells and IL-17A signaling play an important role in host defense and disease development. Th17 cells and IL-17A are critical to the airway immune response against various bacterial and fungal infection [55]. IL-17A may show dual effects on pulmonary arterial thickening and muscularization: IL-13- and IL-17A-induced, and IL-17A-protected via inhibition of IL-13 [26]. IL-13- and the IL-17A-dependent pathways induce the PAH phenotype associated with chronic inflammation [26]. Systemic sclerosis-associated PAH showed correlation between IL-13 and IL-17A, the biomarkers for Th17 and Th2 responses, with disease severity. IL-13-related biomarkers, CD11c and major histocompatibility complex class II (MHC class II, MHC II) expression, RELM- α , RELM- β , matrix metalloproteinase-12, eosinophils and IL-17-related biomarkers, including neutrophils, IL-6, S100a8 and S100a9, have been recognized to be involved in development of PAH [26]. The mechanism by which IL-13 directly induces smooth muscle cell proliferation is questioned, and it is possible to indirectly inactivate inhibitors of mitogen response [26]. An important finding was significant thickening and irregular alignment of pulmonary artery configurations in mice by exposure to only antigen by IL-13. This response occurred in IL-17A-deficient mice, and injection with neutralizing anti-IL-17A antibody significantly exacerbated the severe remodeling response. However, coinjection of neutralizing anti-IL-17A and anti-IL-13 antibodies resulted in apparent inhibition of severe pulmonary arterial remodeling, just like anti-IL-13 antibody alone [26]. Thus, neutralizing IL-13 or IL-17A can be potential therapeutic options for the clinical management of PAH [26].

Experimental research in the rat model revealed that endogenous or externally compressed thrombus could aggravate the expressions of inflammatory mediators [56]. IL-13 increases Rictor level by regulating miR-424/503, leading to an increased migration of the human pulmonary artery endothelial cells [57]. Therefore, thrombolytic and anticoagulant agents would have anti-inflammatory effects or inhibit intimal hyperplasia of the pulmonary arteries and suppress pulmonary vasculature remodeling.

Conclusions

IL-13 is an important regulatory factor that is involved in the pathogenesis of pulmonary vascular remodeling and the development of PAH. The two receptors of IL-13, IL-13R α 1 and IL-13R α 2, play an important role in IL-13 signaling by STAT6 via Jak kinases, and by PI3K, STAT3 and MAPK pathways, respectively. Alternative pathways, including oxidant, Arg2 and hypoxia-inducible factor 1 α might be also involved in the pathological process of PAH development. Investigational therapies have revealed that therapeutic trials by inflammatory suppression or thrombolytic and anticoagulant agents could inhibit intimal hyperplasia of the pulmonary arteries and suppress pulmonary vasculature remodeling. Drug research and development oriented by this theory would surely favor the treatment of PAH.

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