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Review

Inflammation in pulmonary artery hypertension

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1. Introduction

The pathophysiology of pulmonary artery hypertension (PAH) involves a sequence of impairment of pulmonary artery endothelial cells caused by various stresses, pulmonary artery spasm, adhesion and migration of inflammatory cells to the pulmonary artery wall, adventitial fibrosis, intimal occlusive fibrosis, and fibrinoid necrosis leading to plexiform lesion formation. PAH therefore represents a complex yet fascinating interplay of conditions that results in pulmonary vascular remodeling. A clinical classification was established in order to individualize different categories of precapillary pulmonary hypertension (PH) that were identified: PAH(Group 1); PH due to chronic lung disease and/or hypoxia(Group 3); chronic thromboembolic PH(Group 4); some of PH due to unclear multifactorial mechanisms(Group 5), sharing similar pathological findings, similar hemodynamics characteristics [1]. In recent years, greater attention has focused on the frequently-observed perivascular inflammation in patients with all forms of PAH, from idiopathic PAH to PAH associated with systemic autoimmune diseases [2]. Endothelial cells regulate the coagulation-fibrinolysis system, blood vessel permeability, and migration of inflammatory cells, a role that is particularly important to vasoconstriction and expansion. We propose a highly integrated concept of 'vascular failure' that includes a broad spectrum of vascular diseases such as atherosclerosis, vascular endothelial and smooth muscle dysfunction, and metabolic abnormalities of the vessel wall, including inflammation, oxidative stress and alterations in neurohormonal balance [3]. We consider the concept of a 'vascular failure' process may also be applicable to the pulmonary artery, especially in regard to endothelial function and inflammation. Persistent pulmonary vascular endothelial injury and apoptosis is followed by a progressive proliferative phase of phenotypically abnormal endothelium cells, coupled with vascular smooth muscle hypertrophy and vasoconstriction. These pathological changes significantly increase pulmonary vascular resistance and cause pulmonary artery hypertension. Vascular inflammation plays an important role in this process by influencing the pathophysiological mechanisms involved in pulmonary artery hypertension. There is considerable evidence that the levels of circulating inflammatory cytokines such as interleukin (IL)-1α and IL-6 [2] are increased in PAH. More specifically, cellular inflammation results in increases in the number of perivascular macrophages (CD68+), macrophages/monocytes (CD14+), mast cells, dendritic cells (CD209+), T cells (CD3+), cytotoxic T cells (CD8+), and helper T cells (CD4+) in the plexiform lesions of PAH vessels [4]. Regulatory T cell (Treg) controls pulmonary artery endothelial function and possibly inhibits pulmonary vascular remodeling. Increased numbers of circulating Treg cells have been reported in patients with idiopathic PAH [5], whereas reduced numbers of Treg in lung tissue possibly reflect decreased tissue recruitment of these cells. A loss of Treg-mediated self-tolerance leads not only to a loss of T cell tolerance, but also to a breakdown in B cell tolerance. As a result, diminished negative regulation of other active immune cells may trigger or amplify pulmonary vascular remodeling and PAH [6].

Another factor that has emerged as a determinant of the severity of PAH is mutations in bone morphogenesis protein receptor 2 (BMPR2) [7]. Mutations in this receptor have been observed in approximately 70% of subjects with one or more affected relative in a family of patients with heritable PAH and in up to 25% of patients with sporadic idiopathic PAH [8]. A previous study reported that BMPR2 deficiency promoted an exaggerated inflammatory response induced by lipopolysaccharide and initiated the development of PAH, suggesting a potential link between the BMPR2 pathway and inflammation [9]. It is therefore apparent that inflammation is caused in part by a hereditary factor, BMPR2, in patients with PAH.

In the current issue of *Vascular Pharmacology*, Wang et al. [10] focused on the pathophysiological role in PAH of BMPR2 and also high mobility group box 1 (HMGB1), a non-histone nuclear protein that acts as an alarmin to drive the pathogenesis of inflammatory and autoimmune diseases. They showed in a rat model of hypoxia-induced PAH that expression of HMGB1 and toll-like receptor 4 (TLR4) in pulmonary arteries was markedly up-regulated, while expression of BMPR2 signaling was down-regulated. Using cultured primary pulmonary arterial smooth muscle cells, they showed that incubation with HMGB1 significantly promoted the proliferation and migration of pulmonary arterial smooth muscle cells. This effect could be abrogated by HMGB1 and TLR4 inhibitors. Treatment with these inhibitors also significantly attenuated the development of PAH in rats by normalising hemodynamic parameters, pulmonary vascular remodeling and the BMPR2

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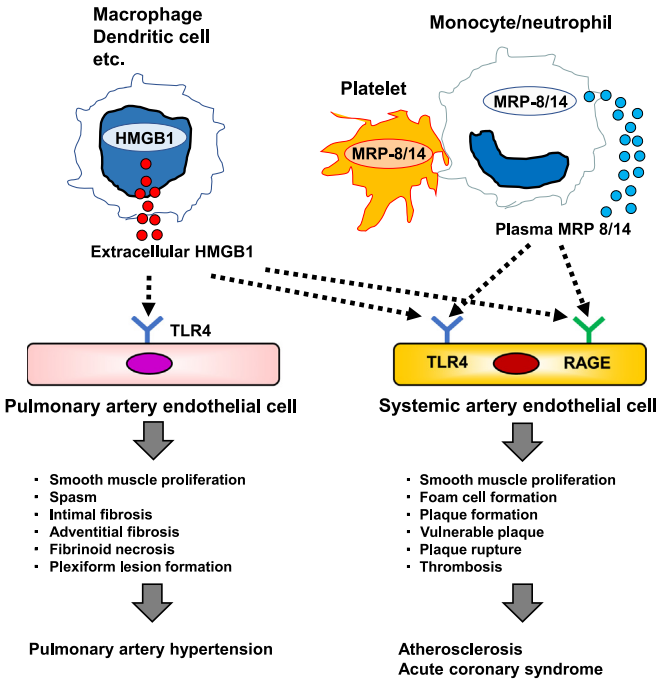

Fig. 1. The roles of alarmins, high mobility group box 1 (HMGB1), and myeloid-related protein-8/14 (MRP-8/14) on the pathophysiology of pulmonary hypertension or atherosclerosis. The HMBG1/toll-like receptor 4 (TLR4) is an important signaling pathway in the pathophysiology of pulmonary hypertension. HMBG1/TLRs signaling and HMBG1/RAGE signaling also play critical roles in atherogenesis and progression of atherosclerosis. During the inflammatory process at the site of vascular injury, such as a ruptured plaque in the coronary artery, MRP-8/14 acts as a promotor of platelet-leukocyte interactions by binding to TLR4 and RAGE.

signaling pathway. These results suggest that HMGB1/TLR4 signaling promotes hypoxia-induced pulmonary hypertension by suppressing the BMPR2 signaling pathway. Prior to Wang et al.'s report Bauer et al. [11] showed that HMGB1 contributed to the pathogenesis of hypoxia-induced PAH by demonstrating extranuclear HMGB1 in pulmonary vascular lesions and increased serum HMGB1 in patients with idiopathic PAH. The increase in circulating HMGB1 correlated with mean pulmonary artery pressure. Genetic deletion of the pattern recognition receptor TLR4 attenuated chronic hypoxia-induced PAH in a mouse model. In addition, treatment with recombinant human HMGB1 exacerbated PAH in wild-type (WT) but not TLR4−/− mice. Taken together, these data suggest that HMGB1-mediated activation of TLR4 promotes experimental PAH and identifies HMGB1/TLR4 as a potential therapeutic target in the treatment of PAH (Fig. 1).

TLR4 is a transmembrane protein member of the TLR family encoded in humans by the TLR4 gene and belongs to the pattern recognition receptor family. TLRs specifically recognize pathogens associated with molecular innate and adaptive immunity. TLRs respond to endogenous host molecules and trigger inflammatory responses. The majority are produced as a result of cell death and injury or by tumor cells, and include degradation products of the extracellular matrix heat-shock proteins and HMGB1 proteins, which act as stimulators for cell surface TLRs. In noninfectious inflammatory diseases such as atherosclerosis and Alzheimer's disease, oxidized low-density lipoprotein and amyloid-β, respectively, trigger sterile inflammation dependent on the activity of TLR4 and TLR6 [12]. Another representative endogenous activator of TLR4 is myeloid-related protein-8/14 (MRP-8/14), a member of the alarmin family, which is similar to HMGB1 and also the S100 family of calcium-modulated proteins. These proteins are expressed in myeloid origin cells, especially in monocytes and neutrophils, and by acting as a chemoattractant and by binding to cell surface receptors including TLR4, they regulate myeloid cell function via modulation of calcium signaling and cytoskeletal reorganization. There is evidence that MRP-8/14 broadly regulates vascular inflammation by binding to TLR4. We demonstrated previously in patients with acute coronary syndrome that MRP-8/14 concentrations were increased in culprit coronary artery blood associated with thrombus formation, and co-localized with leukocytes, neutrophils, and monocytes, leading to leukocyte activation [13]. Another important receptor for MRP-8/14 is advanced glycation end products (RAGE). We consider that during the inflammatory process at the site of vascular injury such as ruptured plaques, MRP-8/14 promotes platelet-leukocyte interactions by binding to TLR4 and RAGE (Fig. 1).

HMGB1 has also been implicated as a proinflammatory mediator in atherosclerotic cardiovascular disease. HMGB1 activates endothelial cells to promote expression of adhesion molecules, concomitant with leukocyte-endothelial adhesion. HMGB1 induces expression of TLR4, nuclear translocation of nuclear factor kappa B (NF-κB), and the binding activity of DNA in endothelial cells. This suggests that the HMGB1/TLR4/NF-κB pathway acts as a cascade between endothelial dysfunction and vascular inflammation in the pathophysiology of atherosclerosis [14]. In addition, extracellular HMGB1 binds both RAGE and TLRs to initiate signaling that culminates in the expression of cytokines such as interleukin (IL)-6 in inflammatory cells [15]. Extracellular HMGB1 is also a key signal molecule in inflammasome activation-mediated foam cell formation. In addition, it has been reported that inflammasome activation-induced HMGB1 activity and foam cell formation were both achieved via RAGE [16]. Taken together, these findings indicate that the HMGB1/TLRs and HMGB1/RAGE signaling pathways play critical roles in the inflammatory process involved in the progression of atherogenesis and atherosclerosis (Fig. 1).

The report by Wang et al. [10] focused on the involvement of the BMPR2 signaling pathway in HMGB1/TLR4 regulated inflammation in PAH. In particular, the specificity of the inhibitory action of TLR4 and denudation toward HMGB1 suggests that it may be possible to prevent HMGB1/TLR4 signaling to BMPR2 signaling in hypoxic PAH. However, more specific signals may be a clinical target in order to enhance substrate specificity. More investigations on these specific signaling pathways are therefore required.

The pulmonary circulation is a low-pressure system, whereas the systemic circulation is a high-pressure system. Because of this difference the anatomical and structural features of the pulmonary artery are different from those of systemic arteries. Diseases of the pulmonary artery and systemic arteries such as peripheral artery disease or coronary artery disease show different etiological and pathophysiological features. However, the two diseases have several common or similar pathophysiological features such as inflammation. In particular, HMGB1/TLR4 signaling may be a very important signaling pathway in the inflammatory process of diseases of both pulmonary and systemic arteries. Further investigations are needed to determine common or similar and different signaling pathways between both types of disease.

References

[1] G. Simonneau, M.A. Gatzoulis, I. Adatia, D. Celermajer, C. Denton, A. Ghofrani, M.A. Gomez Sanchez, R. Krishna Kumar, M. Landzberg, R.F. Machado, H. Olschewski, I.M. Robbins, R. Souza, Updated clinical classification of pulmonary hypertension, J. Am. Coll. Cardiol. 62 (25 Suppl) (2013 Dec 24) D34–D41.
[2] M. Rabinovitch, C. Guignabert, M. Humbert, M.R. Nicolls, Inflammation and immunity in the pathogenesis of pulmonary arterial hypertension, Circ. Res. 115 (1) (2014 Jun 20) 165–175.
[3] T. Inoue, K. Node, Vascular failure: a new clinical entity for vascular disease, J. Hypertens. 24 (2006) 2121–2130.
[4] M. Humbert, G. Monti, F. Brenot, O. Sitbon, A. Portier, L. Grangeot-Keros, P. Duroux, P. Galanaud, G. Simonneau, D. Emilie, Increased interleukin-1 and interleukin-6 serum concentrations in severe primary pulmonary hypertension, Am. J. Respir. Crit. Care Med. 151 (1995) 1628–1631.
[5] R.M. Tuder, B.M. Groves, D.B. Badesch, N.F. Voelkel, Exuberant endothelial cell growth and elements of inflammation are present in plexiform lesions of pulmonary hypertension, Am. J. Pathol. 144 (1994) 275–285.

[6] A. Huertas, L. Tu, N. Gambaryan, B. Girerd, F. Perros, D. Montani, D. Fabre, E. Fadel, S. Eddahibi, S. Cohen-Kaminsky, C. Guignabert, M. Humbert, Leptin and regulatory T-lymphocytes in idiopathicpulmonary arterial hypertension, Eur. Respir. J. 40 (2012) 895–904.
[7] R. Tamosiuniene, W. Tian, G. Dhillon, L. Wang, Y.K. Sung, L. Gera, A.J. Patterson, R. Agrawal, M. Rabinovitch, K. Ambler, C.S. Long, N.F. Voelkel, M.R. Nicolls, Regulatory T cells limit vascular endothelial injury and prevent pulmonary hypertension, Circ. Res. 109 (2011) 867–879.
[8] N.W. Morrell, Pulmonary hypertension due to BMPR2 mutations: a new paradigm for tissue remodeling? Proc. Am. Thorac. Soc. 3 (2006) 680–686.
[9] E. Soon, A. Crosby, M. Southwood, P. Yang, T. Tajsic, M. Toshner, S. Appleby, C.M. Shanahan, K.D. Bloch, J. Pepke-Zaba, P. Upton, N.W. Morrell, Bone morphogenetic protein receptor type II deficiency and increased inflammatory cytokine production. A gateway to pulmonary arterial hypertension, Am. J. Respir. Crit. Care Med. 192 (2015) 859–872.
[10] J. Wang, X.T. Tian, Z. Peng, W.Q. Li, Y.Y. Cao, Y. Li, X.H. Li, HMGB1/TLR4 promotes hypoxic pulmonary hypertension via suppressing BMPR2 signaling, Vasc. Pharmacol. (2019), https://doi.org/10.1016/j.vph.2018.12.006.
[11] E.M. Bauer, R. Shapiro, H. Zheng, F. Ahmad, D. Ishizawar, S.A. Comhair, S.C. Erzurum, T.R. Billiar, P.M. Bauer, High mobility group box 1 contributes to the pathogenesis of experimental pulmonary hypertension via activation of toll-like receptor 4, Mol. Med. 18 (2013) 1509–1518.
[12] T. Kawai, S. Akira, The role of pattern-recognition receptors in innate immunity: update on toll-like receptors, Nat. Immunol. 11 (2010) 373–384.
[13] M. Sakuma, A. Tanaka, N. Kotooka, Y. Hikichi, S. Toyoda, S. Abe, I. Taguchi, K. Node, D.I. Simon, T. Inoue, Myeloid-related protein-8/14 in acute coronary syndrome, Int. J. Cardiol. 249 (2017) 25–31.
[14] J. Yang, C. Huang, J. Yang, H. Jiang, J. Ding, Statins attenuate high mobility group box-1 protein induced vascular endothelial activation: a key role for TLR4/NF-κB signaling pathway, Mol. Cell. Biochem. 345 (2010) 189–195.
[15] A.R. Davalos, M. Kawahara, G.K. Malhotra, N. Schaum, J. Huang, U. Ved, C.M. Beausejour, J.P. Coppe, F. Rodier, J. Campisi, p53-dependent release of Alarmin HMGB1 is a central mediator of senescent phenotypes, J. Cell Biol. 201 (2013) 613–629.
[16] R. Wang, W. Wu, W. Li, S. Huang, Z. Li, R. Liu, Z. Shan, C. Zhang, W. Li, S. Wang, Activation of NLRP3 inflammasome promotes foam cell formation in vascular smooth muscle cells and atherogenesis via HMGB1, J. Am. Heart Assoc. 7 (2018) e008596, , https://doi.org/10.1161/JAHA.118.008596.