

## Is Elevated Circulating Galectin-3 Level A Predictor of Pulmonary Artery Hypertension Development and Progression?

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### Abstract

Pulmonary arterial hypertension (PAH) is a heterogenic group of devastating disorders that characterizes higher rates of mortality and morbidity worldwide. Recent clinical studies have shown that clinical features, hemodynamic parameters, echocardiography pattern, multi-spiral computer tomography findings, exercise capacity, and anti-nuclear antibody profiles could be used as predictors of clinical severity and outcomes in PAH patients. However, the reliability, sensitivity, specificity and predictive value are derived from PAH patients with different comorbidities and specific complications associated with connective tissue disease (CTD), congenital heart disease and respiratory disease might be unacceptable. The aim of the mini review: to summarize the knowledge regarding predictive value of galectin-3 as a biomarker in PAH individuals. The mini review is argued the perspective to utilize single sample and serial measurements of Gal-3 as a regulatory peptide contributed in PAH pathogenesis aimed to improve prediction of PAH development and progression.

**Keywords:** Pulmonary artery hypertension; Galectin-3; Biomarkers; Prognostication

### Introduction

Pulmonary arterial hypertension (PAH) is a heterogenic group of distinct disorders that includes idiopathic PAH (IPAH), familial PAH and PAH associated with other conditions (APAH) such as connective tissue disease (CTD-APAH), respiratory disease, congenital or acquired left-heart inflow/outflow obstructive lesions or congenital cardiomyopathies etc. [1,2]. PAH is characterized by pulmonary capillary endothelial metabolic dysfunction directly related to microvascular inflammation that leads to increased pulmonary arterial pressure and pulmonary vascular resistance [3-5]. Despite histological findings that are suitable for the pulmonary vascular lesions in PAH complicating CTD are similar to those observed in IPAH, familial PAH and APAH, morbidity and mortality rates between these patient cohorts sufficiently distinguish. Compared with IPAH patients and familial PAH individuals, patients with PAH associated with CTD have an older age of onset and exhibited worse prognosis in survival [6]. Survival of patients with respiratory disease-related or congenital heart disease-related PAH in the modern treatment era is better than CTD-APAH [6,7]. Although clinical features, hemodynamic parameters, echocardiography pattern, multi-spiral computer tomography findings, exercise capacity, and anti-nuclear antibody profiles were found as powerful factors predicted a development of PAH due to several diseases [8], the reliability, sensitivity, specificity and predictive value are derived from PAH patients with different comorbidities and specific complications associated with CTD, congenital heart disease and respiratory disease might be unacceptable [9]. In this context, taken into consideration pathophysiological heterogeneity of PAH to risk stratification based on biological markers (N-terminal pro-brain natriuretic peptide, red cell distribution width, soluble endoglin, growth differentiation factor-15, interleukin-6, soluble vascular endothelial growth factor receptor-1, C-reactive protein, pentraxin 3) reflected several faces of nature evolution of the disease might be useful and appears to be attractive [10-13]. Although several biomarkers are widely investigated for risk stratification around patients with PAH, there are several limitations to clinical use associating with higher biological variability and cost, low specificity, lack direct evidence regarding prediction of clinical status and outcomes. However, the discovery of biomarkers that might sufficiently improve of prediction of traditional approaches and personalize of the medical care appears to be attractive.

Galectin-3 (Gal-3) has been found a soluble beta galactoside-binding lectin produced by activated macrophages which binds and activates the fibroblasts leading to the deposition of collagen into the extracellular matrix and to a progressive cardiovascular fibrosis [14]. Recent pre-clinical and clinical studies have been indicated an important role for Gal-3 signaling mechanism in the pathophysiology of IPAH and PAH-CTD [15,16]. Moreover, Gal-3 acts a fundamental regulator of inflammation, fibrosis, angiogenesis, adhesion, tumor growth and progression, and immunological functions [17-19]. There is evidence regarding independent association between Gal-3 levels and microalbuminuria, an early marker of endothelial dysfunction and altered renal function [20]. Ho et al. [21] have reported that elevated Gal-3 concentrations are closely associated with interstitial lung abnormalities, coupled with a restrictive pattern including decreased lung volumes and altered gas exchange. On the other hand, nitric oxide synthases-2-derived nitrogen oxides seem to play an important role in inflammatory regulation through Gal-3 expression in restrictive lung disease and interstitial lung abnormalities [22]. Because inflammation, fibrosis, endothelial dysfunction and cell adhesion are involved in the pathogenesis of both IPAH and PAH-CTD, it has been suggested that Gal-3 may serve as biomarkers for functional status and progression of disease [15]. The aim of the mini review: to summarize the knowledge regarding predictive value of galectin-3 as a biomarker in PAH individuals.

### The Biological Role and Function of Galectin-3

Gal-3 is a multifunctional adhesion-modulated and growth-regulatory  $\beta$ -galactoside-binding lectin that secreted by activated mononuclears / macrophages and contributed to various

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pathophysiological processes affected cardiac / vascular remodeling, cardiac fibrosis, and inflammation [17]. As a multifactorial regulator of cell function Gal-3 is involved in cell proliferation / differentiation, angiogenesis, neovascularization, as well as malignancy, tumor cell adhesion and metastasis [18]. The main regulators of Gal-3 secretion are pro-inflammatory cytokines, i.e., interferon- $\gamma$ , tumor necrosis factor alpha, and interleukin-17, components of oxidative stress, free radicals, aldosterone, and transforming growth factor-beta [19].

Recent studies have shown that Gal-3 exhibits a pro-inflammatory response by recruiting and activating lymphocytes, mononuclears / macrophages and other antigen-presenting cells [23,24]. Indeed, Gal-3 galectin-3 exerts cytokine-like regulatory actions on production of inflammasome via activation of the JAK-STAT cascade [25]. Vergaro et al. [26] reported that Gal-3 may interact with aldosterone in promoting macrophage infiltration and vascular fibrosis. Therefore, Gal-3 contributes to cardio renal remodeling and endothelial dysfunction induced by aldosterone [27]. Interestingly, in animal models Gal-3 not only causes cardiac hypertrophy, but directly induces cardiac dysfunction through involvement of the transforming growth factor (TGF)-beta/Smad3 signaling pathway [28-30]. Moreover, inhibition of Gal-3 was associated with a down-regulation in collagen I and III production, collagen processing, cleavage, cross-linking, and deposition [31]. Taken together these data have suggested that Gal-3 could be a novel therapeutic target in cardiac fibrosis and inflammation, while clinical relevance of these findings requires more investigations.

Recent study has shown that Gal-3 appears to be localized on the osteoclast cell surface, and its suppression sufficiently inhibited osteoclast differentiation and reduced the number of mature osteoclasts [32]. These findings elucidate the role of Gal-3 in modulation of bone mineralization/osteoporosis and link the process with inflammation. Finally, Gal-3 signaling is argued as an important mechanism of cardiac/vascular remodeling development based on inducing of hypertrophy/fibrosis and inflammation.

### Galectin-3 Signaling in PAH

PAH is characterized by abnormal elaboration of vasoactive substance (endothelin-1, serotonin, bone morphogenetic proteins, Rho kinase, and hypoxia-inducible factor 1), endothelial cell dysfunction, vascular remodeling, and inflammation, which collectively contribute to its pathogenesis [33]. Overall, pathogenetic transformation of the pulmonary vascular bed is argued a main cause of PAH development with and without associated various clinical phenotypes. Indeed, despite the pathogenesis of PAH is a complex and multifactorial process, inflammation could be a trigger of endothelial injury, pulmonary artery smooth muscle cell proliferation, chemoattractant over-production [4]. There is evidence regarding the role of pulmonary arterial smooth muscle and endothelial cells in vasoconstriction, development of vaso-occlusive lesions and ventilation-perfusion mismatch [34]. Therefore, PAH might occur due to several molecular mechanisms resulting in heterogeneous genetic defects affecting defects of the transforming growth factor beta pathway that could be regulated with Gal-3 [35]. At this pathway, Gal-3 may play a pivotal role in establishment and progression of PAH via inducing of endothelial dysfunction and hyperplasia of the underlying medial layer potentially through direct activation of (TGF)-beta/Smad3 signaling.

### Elevated Galectin-3 Level and Cardiovascular Events

Elevated levels of circulating Gal-3 has found in cardiovascular (CV) disease (coronary artery disease, hypertension, heart failure, atrial fibrillation / flutter), renal and metabolic (diabetes mellitus,

metabolic syndrome, obesity) disease and were strongly associated with asymptomatic atherosclerosis, premature CV events including myocardial infarction, acute / acutely decompensated heart failure, and sudden death [36-39]. In general population increased Gal-3 concentrations were found as predictor of CV disease and diabetes development [40,41]. Furthermore, Gal-3 has potential relations with CV mortality and all-cause mortality beyond classical and new markers of CV risk [42,43]. However, the predictive role of Gal-3 in PAH individuals are still not fully clear.

### Predictive Value of Galectin-3 in PAH

The heterogeneity of nature evolution, clinical features, prognosis, and treatment response supports the need for identifying PAH patients at risk with various methods [44]. Recent clinical studies have shown that clinical status, hemodynamics, several biomarkers (growth differentiation factor-15, interleukin-6, creatinine, and NT-proBNP levels) and exercise capacity may predict severity and clinical outcomes in selected cohorts of patients with PAH [11] including subjects with known cardiac dysfunction [45]. However, lack of universal predictive model mediate to discovery of novel biomarkers and / or utilize a multi biomarker approaches. In this context, predictive model based on Gal-3 single sample measurements could be useful for risk stratification of PAH individuals. Moreover, serial measurements of Gal-3 within treatment are argued a perspective tool for assay the positive response in long-term period affecting mortality rate in PAH. Indeed, Calvier et al. [15] reported that elevated level of Gal-3 was closely associated with severity of PAH independently etiology. Fenster et al. [16] presented evidence regarding sufficient relation between circulating level of Gal-3 and morphologic changes in PAH including estimate right ventricle (RV) systolic pressure and measure RV strain. Authors found that Gal-3 positively correlated with the extracellular matrix markers, i.e., tissue inhibitor of metalloproteinase-1 (TIMP-1), and hyaluronic acid. However, the evidence regarding multi maker strategy to identify patients at higher risk of PAH development and complications are very limited and requires a confirmation in the large clinical trials.

In conclusion, Gal-3 is crucial to the development of the acute and chronic inflammatory response to endothelial injury, it is also necessary to vascular remodeling associated with marked fibrosis. However, Gal-3 might over-express in the interstitial lung tissue and in the pulmonary vasculature due to several causes and associates closely with endothelial dysfunction, worsening of vascular integrity, and PAH development. Despite an increased interest in Gal-3 as a regulatory peptide contributed in PAH pathogenesis, there are no significant evidence regarding both single sample and serial measurements of this biomarkers aimed to improve prediction of PAH development and progression. More clinical trials are needed to explain the predictive role of Gal-3 in PAH individuals with several etiology.

### References

1. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, et al. (2013) Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol* 62: D42-50.
2. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, et al. (2013) Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 62: D34-41.
3. Pagán RJ, Lee AS, Austin CO, Burger CD (2014) Screening for connective tissue disease in pulmonary arterial hypertension. *South Med J* 107: 666-669.
4. Langleben D, Orfanos SE, Giovannazzo M, Hirsch A, Baron M, et al. (2008) Pulmonary capillary endothelial metabolic dysfunction: severity in pulmonary arterial hypertension related to connective tissue disease versus idiopathic pulmonary arterial hypertension. *Arthritis Rheum* 58: 1156-1164.

5. Tamura Y, Ono T, Kuwana M, Inoue K, Takei M, et al. (2012) Human pentraxin 3 (PTX3) as a novel biomarker for the diagnosis of pulmonary arterial hypertension. *PLoS One* 7: e45834.
6. Sadeghi S, Granton JT, Akhavan P, Pasarikovski CR, Roos AM, et al. (2015) Survival in rheumatoid arthritis-associated pulmonary arterial hypertension compared with idiopathic pulmonary arterial hypertension. *Respirology* 20: 481-487.
7. Condliffe R, Kiely DG, Peacock AJ, Corris PA, Gibbs JS, et al. (2009) Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. *Am J Respir Crit Care Med* 179: 151-157.
8. Shirai Y, Yasuoka H, Okano Y, Takeuchi T, Satoh T, et al. (2012) Clinical characteristics and survival of Japanese patients with connective tissue disease and pulmonary arterial hypertension: a single-centre cohort. *Rheumatology (Oxford)* 51: 1846-1854.
9. Hassoun PM (2009) Pulmonary arterial hypertension complicating connective tissue diseases. *Semin Respir Crit Care Med* 30: 429-439.
10. Grunig G, Baghdassarian A, Park SH, Pylawka S, Bleck B, et al. (2016) Challenges and Current Efforts in the Development of Biomarkers for Chronic Inflammatory and Remodeling Conditions of the Lungs. *Biomark Insights* 10: 59-72.
11. Rhodes CJ, Wharton J, Howard LS, Gibbs JS, Wilkins MR (2011) Red cell distribution width outperforms other potential circulating biomarkers in predicting survival in idiopathic pulmonary arterial hypertension. *Heart* 97: 1054-1060.
12. Mathai SC, Bueso M, Hummers LK, Boyce D, Lechtzin N, et al. (2010) Disproportionate elevation of N-terminal pro-brain natriuretic peptide in scleroderma-related pulmonary hypertension. *Eur Respir J* 35: 95-104.
13. Malhotra R, Paskin-Flerlage S, Zamanian RT, Zimmerman P, Schmidt JW, et al. (2013) Circulating angiogenic modulatory factors predict survival and functional class in pulmonary arterial hypertension. *Pulm Circ* 3: 369-380.
14. Giannakoulas G, Mouratoglou SA, Gatzoulis MA, Karvounis H (2014) Blood biomarkers and their potential role in pulmonary arterial hypertension associated with congenital heart disease. A systematic review. *Int J Cardiol* 174: 618-623.
15. Calvier L, Legchenko E, Grimm L, Sallmon H, Hatch A, et al. (2016) Galectin-3 and aldosterone as potential tandem biomarkers in pulmonary arterial hypertension. *Heart* 102: 390-396.
16. Fenster BE, Lasalvia L, Schroeder JD, Smyser J, Silveira LJ, et al. (2015) Galectin-3 levels are associated with right ventricular functional and morphologic changes in pulmonary arterial hypertension. *Heart Vessels*.
17. Li LC, Li J, Gao J (2014) Functions of galectin-3 and its role in fibrotic diseases. *J Pharmacol Exp Ther* 351: 336-343.
18. Wang L, Guo XL (2016) Molecular regulation of galectin-3 expression and therapeutic implication in cancer progression. *Biomed Pharmacother* 78: 165-171.
19. Radosavljevic G, Volarevic V, Jovanovic I, Milovanovic M, Pejnovic N, et al. (2012) The roles of Galectin-3 in autoimmunity and tumor progression. *Immunol Res* 52: 100-110.
20. Iacoviello M, Aspromonte N, Leone M, Paradies V, Antoncicchi V, et al. (2015) Galectin-3 Serum Levels Are Independently Associated With Microalbuminuria in Chronic Heart Failure Outpatients. *Res Cardiovasc Med* 5: e28952.
21. Ho JE, Gao W, Levy D, Santhanakrishnan R, Araki T, et al. (2016) Galectin-3 is Associated with Restrictive Lung Disease and Interstitial Lung Abnormalities. *Am J Respir Crit Care Med*.
22. Guo C, Atochina-Vasserman E, Abramova H, George B, Manoj V, et al. (2016) Role of NOS2 in pulmonary injury and repair in response to bleomycin. *Free Radic Biol Med* 91: 293-301.
23. Jia W, Kidoya H, Yamakawa D, Naito H, Takakura N (2013) Galectin-3 accelerates M2 macrophage infiltration and angiogenesis in tumors. *Am J Pathol* 182: 1821-1831.
24. Simovic Markovic B, Nikolic A, Gazdic M, Bojic S, Vucicevic L, et al. (2016) Galectin-3 Plays an Important Pro-inflammatory Role in the Induction Phase of Acute Colitis by Promoting Activation of NLRP3 Inflammasome and Production of IL-1 $\beta$  in Macrophages. *J Crohns Colitis*.
25. Jeon SB, Yoon HJ, Chang CY, Koh HS, Jeon SH, et al. (2010) Galectin-3 exerts cytokine-like regulatory actions through the JAK-STAT pathway. *J Immunol* 185: 7037-7046.
26. Vergaro G, Prud'homme M, Fazal L, Merval R, Passino C, et al. (2016) Inhibition of Galectin-3 Pathway Prevents Isoproterenol-Induced Left Ventricular Dysfunction and Fibrosis in Mice. *Hypertension* 67: 606-612.
27. Calvier L, Martínez-Martínez E, Miana M, Cachafeiro V, Rousseau E, et al. (2015) The impact of galectin-3 inhibition on aldosterone-induced cardiac and renal injuries. *JACC Heart Fail* 3: 59-67.
28. Liu YH, D'Ambrosio M, Liao TD, Peng H, Rhaleb NE, et al. (2009) N-acetylseryl-aspartyl-lysyl-proline prevents cardiac remodeling and dysfunction induced by galectin-3, a mammalian adhesion/growth-regulatory lectin. *Am J Physiol Heart Circ Physiol* 296: H404-H412.
29. Martínez-Martínez E, Calvier L, Fernández-Celis A, Rousseau E, Jurado-López R, et al. (2015) Galectin-3 blockade inhibits cardiac inflammation and fibrosis in experimental hyperaldosteronism and hypertension. *Hypertension* 66: 767-775.
30. Martínez-Martínez E, López-Ándres N, Jurado-López R, Rousseau E, Bartolomé MV, et al. (2015) Galectin-3 Participates in Cardiovascular Remodeling Associated With Obesity. *Hypertension* 66: 961-969.
31. Yu L, Ruffrok WP, Meissner M, Bos EM, van Goor H, et al. (2013) Genetic and pharmacological inhibition of galectin-3 prevents cardiac remodeling by interfering with myocardial fibrogenesis. *Circ Heart Fail* 6: 107-117.
32. Nakajima K, Kho DH, Yanagawa T, Harazono Y, Hogan V, et al. (2016) Galectin-3 Cleavage Alters Bone Remodeling: Different Outcomes in Breast and Prostate Cancer Skeletal Metastasis. *Cancer Res* 76: 1391-1402.
33. Shimoda LA, Laurie SS (2013) Vascular remodeling in pulmonary hypertension. *J Mol Med (Berl)* 91: 297-309.
34. Evans AM, Lewis SA, Ogunbayo OA, Moral-Sanz J (2015) Modulation of the LKB1-AMPK Signalling Pathway Underpins Hypoxic Pulmonary Vasoconstriction and Pulmonary Hypertension. *Adv Exp Med Biol* 860: 89-99.
35. Machado RD, Southgate L, Eichstaedt CA, et al. (2015) Pulmonary Arterial Hypertension: A Current Perspective on Established and Emerging Molecular Genetic Defects. *Hum Mutat* 36: 1113-1127.
36. Berezin AE (2015) The Role of Cardiac Biomarkers in Predicting of Mortality in Diabetic Patients. *J Cardiology and Therapy* 2: 400-404.
37. Winter MP, Wiesbauer F, Alimohammadi A, Blessberger H, Pavo N, et al. (2016) Soluble Galectin-3 is Associated with Premature Myocardial Infarction. *Eur J Clin Invest*.
38. Chen YS, Gi WT, Liao TY, Lee MT, Lee SH, et al. (2016) Using the galectin-3 test to predict mortality in heart failure patients: a systematic review and meta-analysis. *Biomark Med* 10: 329-342.
39. Martínez-Martínez E, Calvier L, Rossignol P, Rousseau E, Fernández-Celis A, et al. (2016) Galectin-3 inhibition prevents adipose tissue remodeling in obesity. *Int J Obes (Lond)*.
40. Pugliese G, Iacobini C, Ricci C, Blasetti Fantauzzi C, Menini S (2014) Galectin-3 in diabetic patients. *Clin Chem Lab Med* 52: 1413-1423.
41. Menini S, Iacobini C, Blasetti Fantauzzi C, Pesce CM, Pugliese G (2016) Role of Galectin-3 in Obesity and Impaired Glucose Homeostasis. *Oxid Med Cell Longev* 2016: 9618092.
42. Lisowska A, Knapp M, Tycinska A, Motybel E, Kaminski K, swiecki P, et al. (2016) Predictive value of Galectin-3 for the occurrence of coronary artery disease and prognosis after myocardial infarction and its association with carotid IMT values in these patients: A mid-term prospective cohort study. *Atherosclerosis* 246: 309-317.
43. Hogas S, Schiller A, Voroneanu L, Constantinescu D, Timar R, et al. (2016) Predictive Value for Galectin 3 and Cardiotrophin 1 in Hemodialysis Patients. *Angiology*.
44. Berezin AE (2016) Elevated galectin-3 level predicts pulmonary artery hypertension. *Biological Markers and Guided Therapy* 3: 89-97.
45. Leone M, Iacoviello M (2016) The predictive value of plasma biomarkers in discharged heart failure patients: role of galectin-3. *Minerva Cardioangiol* 64: 181-194.

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