Pulmonary Arterial Hypertension

Subjects: Others

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Recognition of and response to pathogens and tissue injury is driven by the innate immune system via activation of pattern recognition receptors. One of the many patterns recognized is RNA and, while several receptors bind RNA, Toll-like receptor 3 (TLR3) is well placed for initial recognition of RNA molecules due to its localization within the endosome. There is a growing body of work describing a role for TLR3 in maintenance of vascular homeostasis. For example, TLR3 deficiency has been shown to play repair and remodeling roles in the systemic vasculature and in lung parenchyma. A hallmark of pulmonary arterial hypertension (PAH) is pulmonary vascular remodeling, yet drivers and triggers of this remodeling remain incompletely understood. Based on its role in the systemic vasculature, our group discovered reduced endothelial TLR3 expression in PAH and revealed a protective role for a TLR3 agonist in rodent models of pulmonary hypertension.

Pulmonary arterial hypertension | Toll-like receptor | TLR3 | double-stranded RNA | RNA sensors | vascular remodeling

1. Background

Tremendous effort has been put forward into understanding dysregulated pathways in pulmonary arterial hypertension (PAH) and these investigations span numerous topics including genetics, growth factors, metabolism and inflammation[1]. Links between inflammation and PAH are strong, although the role of the innate immune system in the initiation or propagation of vascular remodeling remains incompletely defined.

Over the past two decades, we have come to understand that innate immunity is of fundamental importance as not only the first line of defense from external pathogens, but in protection from cellular injury and maintenance of tissue homeostasis. Stemming from Janeway's concept of "pattern recognition receptors" (PRRs) that bind "pathogen-associated molecular patterns" (PAMPs), ongoing research has found that PRRs also recognize internal "damage-associated molecular patterns" (DAMPs) [2]. Whereas PAMPs were bits and pieces that came from processing of pathogens by the immune system, DAMPs are frequently part of the structural and functional components of our own cells and tissues, which are released during tissue injury. RNA has emerged as an important intracellular DAMP [3].

2. Toll-like Receptor 3 (TLR3)

In recent years, Toll-like receptor 3 (TLR3) has been established as a central PRR for all sorts of RNA molecules. Principally recognized as a viral double-stranded RNA (dsRNA) sensor, TLR3 also responds to synthetic dsRNA such as polyinosinic:polycytidylic acid [poly(I:C)] and to endogenous mRNA and has been implicated in tissue repair and remodeling in a number of experimental settings [4][5].

TLR3 signaling in pulmonary arterial hypertension

We revealed evidence of loss of TLR3 expression in pulmonary artery endothelial cells (PAECs) from patients with PAH and in animal models. of pulmonary hypertension [6]. TLR3 knockout mice developed more severe disease, with higher right ventricular systolic pressure (RVSP) and evidence of greater small pulmonary artery muscularization. CRISPR/cas9-mediated reduction in TLR3 protein level was associated with increased endothelial cell apoptosis, mirroring evidence of apoptosis susceptibility in PAECs from patients with PAH. Interestingly, the TLR3 agonist, poly(I:C), increased TLR3 expression in rat lung ECs in an IL-10 dependent manner. Prophylactic high-dose poly(I:C) treatment in the hypoxia and SU5416 PH rat model reduced RVSP and the number of vascular occlusions, but had no significant effect on medial wall thickness or cardiac output. Therapeutic poly(I:C) attenuated established PH when administered 3 weeks after initiation of the disease with hypoxia and SU5416. With both prophylactic and therapeutic poly(I:C) treatment, the number of apoptotic and proliferative cells in the pulmonary arteries were significantly reduced. These data suggest that the TLR3-agonist, poly(I:C), can restore TLR3 levels in TLR3 deficient endothelial cells, thus restoring protective anti-remodeling signals mediated via this pathway.However, there are potentially detrimental consequences associated with activating double-stranded RNA signaling and these are highlighted in our review article [7]. For example, overactivity of this pathway or excessive production of downstream effectors such as interferons (IFN), endothelin-1, and pro-inflammatory cytokines may result in endothelial cell dysfunction and could thus contribute to pulmonary hypertension pathogenesis.

3. Conclusions

Gaps in our knowledge of dsRNA signaling need to be filled before exploring poly(I:C) as a therapy in PAH. It is not known whether the protective effects of synthetic dsRNA in the rodent models were mediated via TLR3 signaling in the pulmonary vascular tissue or whether other TLR3-expressing perivascular or circulating leukocytes are important. Furthermore, activation of TLR3 signaling has been associated with upregulation of other dsRNA sensors. Yet how these contribute to protective vascular phenotypes in PAH has not been investigated.

There appears to be a finely tuned balance between protective innate immune responses to dsRNA and potentially detrimental pro-inflammatory signals from receptors activated by the same stimulus. The complexity of the relationship between vascular protection mediated by dsRNA and adverse associations between pulmonary vascular disease and interferon treatment casts doubt on whether targeting this pathway will translate as a treatment for PAH. However, strategies to enhance TLR3 signaling could be developed with synergistic targeting of excessive IFN activity. Now that dsRNA receptor agonists, such as rintatolimod (Ampligen), are emerging in other

contexts as safe adjuvants for cancer therapies and for other conditions such as chronic fatigue syndrome, we believe that exploration of dsRNA as a therapy merits further evaluation in cellular and animal models of PAH.

References

1. A. A. Roger Thomson; Allan Lawrie; Targeting Vascular Remodeling to Treat Pulmonary Arterial Hypertension. *Trends in Molecular Medicine* **2017**, *23*, 31-45, 10.1016/j.molmed.2016.11.005.
2. Ruslan Medzhitov; Charles A. Janeway; Innate immunity: the virtues of a nonclonal system of recognition.. *Cell* **1997**, *91*, 295-298, 10.1016/s0092-8674(00)80412-2.
3. Katalin Kariko; Houping Ni; John Capodici; Marc Lamphier; Drew Weissman; mRNA Is an Endogenous Ligand for Toll-like Receptor 3. *Journal of Biological Chemistry* **2004**, *279*, 12542-12550, 10.1074/jbc.m310175200.
4. Jennifer Cole; Tina J. Navin; Amanda J. Cross; Michael E. Goddard; Lena Alexopoulou; Anuja T. Mitra; Alun H. Davies; Richard A. Flavell; Marc Feldmann; Claudia Monaco; et al. Unexpected protective role for Toll-like receptor 3 in the arterial wall. *Proceedings of the National Academy of Sciences* **2011**, *108*, 2372-2377, 10.1073/pnas.1018515108.
5. David N. O'Dwyer; Michelle E. Armstrong; Glenda Trujillo; Gordon Cooke; Michael P. Keane; Padraic Fallon; A. John Simpson; Ann B. Millar; Emmet E. McGrath; Moira K. Whyte; et al.Nik HiraniCory M. HogaboamSeamas C. Donnelly The Toll-like Receptor 3 L412F Polymorphism and Disease Progression in Idiopathic Pulmonary Fibrosis. *American Journal of Respiratory and Critical Care Medicine* **2013**, *188*, 1442-1450, 10.1164/rccm.201304-0760oc.
6. Daniela Farkas; A. A. Roger Thomson; Aneel R. Bhagwani; Schuyler Hultman; Hyun Ji; Naveen Kotha; Grant Farr; Nadine D. Arnold; Adam Braithwaite; Helen Casbolt; et al.Jennifer ColeIan SabroeClaudia MonacoCarlyne D. CoolElena A. GoncharovaAllan LawrieLaszlo Farkas Toll-like Receptor 3 Is a Therapeutic Target for Pulmonary Hypertension. *American Journal of Respiratory and Critical Care Medicine* **2019**, *199*, 199-210, 10.1164/rccm.201707-1370oc.
7. Helena A. Turton; A. A. Roger Thomson; Laszlo Farkas; RNA Signaling in Pulmonary Arterial Hypertension-A Double-Stranded Sword.. *International Journal of Molecular Sciences* **2020**, *21*, 3124, 10.3390/ijms21093124.