Hungry for More

Autophagy in the Pathogenesis of Pulmonary Arterial Hypertension

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Genetic alterations in pulmonary arterial hypertension (PAH) have become increasingly recognized in both known familial or heritable and sporadic or idiopathic PAH (IPAH). Unrecognized genetic alterations have now been found in up to 40% of the IPAH in which no familial predisposition is apparent. Bone morphogenetic protein (BMP) receptor II (BMPR-II) is the most common gene implicated in this hereditary form of PAH; furthermore, it is implicated in the pathogenesis of nonhereditary forms of PAH with a significant reduction in the expression of BMPR-II in both IPAH and experimental animal models of pulmonary hypertension (PH). BMPs represent the largest group of cytokines in the transforming growth factor-β superfamily and regulate growth, differentiation, and apoptosis in multiple cell types, whereas BMPR-II has been shown to have unique roles in differing cells.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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Circulation Research is available at http://circres.ahajournals.org
DOI: 10.1161/CIRCRESAHA.113.301247

In IPAH, autophagy has been shown to be upregulated, with the marker for mature autophagosomes, light chain 3B (LC3B)-II, having increased expression compared with healthy controls. The role of autophagy in PH remains inconclusive but seems to be important in vascular remodeling. Pulmonary artery endothelial cells exposed to hypoxia have increased autophagy, which is thought to be a protective mechanism, because LC3B-II knockout mice have exaggerated PH in response to chronic hypoxia. In contrast, persistent PH in fetal lambs, an experiment model of persistent PH of the newborn, is associated with increased autophagy thought to be detrimental to fetal angiogenesis, inhibiting autophagy can lead to restoration of adequate angiogenesis. Yet, as with any highly regulated cellular mechanism, proper cellular balance seems to be essential for normal function, and these early data have confirmed the complicated nature of autophagy in disease processes. This seems to be the case with regard to BMPR-II and autophagy. Previous work by Morrellet al has shown that the lower levels of BMPR-II seen in experimental models of PH seem to be at least in part attributable to BMPR-II being targeted for ubiquitination and degradation via the lysosome (Figure).

In this issue of Circulation Research, Long et al discuss the role of autophagy and lysosomal BMPR-II degradation in the pathogenesis of experimental PH. They provide new evidence...
linking increased autophagy with downregulation of BMPR-II/Smad pathway in the development of PAH. In a disease in which new therapeutic targets are desperately needed, this may well be a novel target. The authors were able to show both prevention and partial reversal of monocrotaline-induced PH in rats using chloroquine, an inhibitor of autophagy. They further were able to show that the effect of chloroquine was through inhibition of autophagy both in vivo and in vitro, with downstream effects resulting in reduced proliferation and increased apoptosis of pulmonary arterial smooth muscle cells. The diminished protein expression of BMPR-II and Smad signaling in this experimental rat model of PH was restored with the use of chloroquine. This inhibition of autophagy and lysosomal degradation is established in vitro by using knockdown of autophagy-specific ATG5 and concanamycin A treatment, a specific inhibitor of lysosomal degradation, which were both associated with increased expression of BMPR-II and decreased LC3B-II. The authors have concluded that chloroquine ameliorates monocrotaline-induced PH in the rat and that this effect is mediated through downregulated autophagy inhibiting lysosomal degradation of BMPR-II.

The results from this study represent very interesting insight into the potential mechanism of attenuated BMPR-II expression in human PAH. Enhanced autophagy and lysosomal degradation may be a novel pathogenic mechanism and potential therapeutic target for this disease. A compound that has made a resurgence of late, chloroquine and its less toxic cousin, hydroxychloroquine, have remained mainstays in malaria treatment and chemoprophylaxis, and the steroid-sparing anti-inflammatory effects of these medications have proved useful in systemic lupus erythematosus, rheumatoid arthritis, and sarcoidosis. Repurposing of a medication that is both well tolerated and inexpensive makes it an attractive agent to clinicians, especially to physicians in the developing countries where the commonly used drugs for PAH are not available. The present results provide a plausible mechanism by which experimental PAH was both prevented and reversed, yet both chloroquine and hydroxychloroquine have multiple known and unknown cellular and molecular targets in the human body, and it is unlikely that inhibition of autophagy is the sole effect on the pulmonary vasculature.

There are growing data on the role of inflammation in PAH. Cytokines, particularly interleukin-6, have largely been implicated in the disease process, affecting both vascular remodeling and vasoconstriction, which should not be unexpected, given the similarities between IPAH and associated PAH as a result of chronic inflammatory disorders such as systemic lupus erythematosus, rheumatoid arthritis, and systemic sclerosis. The fact that hydroxychloroquine has in more recent years been found to be a significant immunomodulator with steroid-sparing effects that are beneficial in many of these diseases would potentially implicate its anti-inflammatory properties in the treatment of PAH. Indeed, because hydroxychloroquine treatment is associated with reduced levels of interleukin-6 in patients with systemic lupus erythematosus, it would be reasonable to assume similar effects in the pulmonary vasculature, which could have potential benefits in a disease characterized by inflammation and elevated interleukin-6 levels, although studies are lacking at this time. This immunomodulatory effect may also be contributing to PAH prevention and reversal.

Figure. Proposed role of autophagy in bone morphogenetic protein (BMP) receptor (BMPR)-II downregulation in pulmonary arterial hypertension (PAH). Decreased BMPR-II protein levels in pulmonary vascular smooth muscle and endothelial cells are observed in patients with idiopathic PAH and animals with experimental pulmonary hypertension. Long et al.14 proposed a mechanism in which BMPR-II is internalized from the plasma membrane and ubiquitinated. The ubiquitinated BMPR-II protein is then engulfed by the autophagosome and degraded through a lysosomal-mediated pathway. LC3B indicates light chain 3B.
in this animal model, although this effect would still support potential clinical efficacy and safety trials in human patients.

Animal models have always presented problems in research. The complexity of PAH makes this particularly challenging, and experimental models are invariably flawed. Monocrotaline, a plant-derived pyrrolizidine alkaloid, leads to endothelial cell dysfunction and vascular remodeling through unclear mechanisms, although many believe that inflammatory mechanisms play an important role in the pathogenesis of monocrotaline-induced experimental PH. Given the propensity for an exaggerated inflammatory response, it may not represent an ideal model of PAH and would presumably give preference to therapeutics agents with immune-related effects, although other experimental models such as hypoxia-induced PH or Sugen/hypoxia-mediated PH are not without their limitations. It is more likely that these models each emphasize a small part of a large and complicated disease process, and using them in a complementary manner may likely provide better insight into a disease process than simply using a single model alone.

The complexity of human disease is becoming ever apparent. New and exciting molecular pathways and pathogenic mechanisms have met with both success and failure in translation to real-world disease. The complexity that surrounds PAH and BMPR-II, in particular, makes it reasonable to assume that the answer will not come in a single pill. Still, with the undeniable knowledge that this single receptor plays such an important role in the pathogenesis of PAH, each new discovery is a piece of the puzzle leading to a potential cure. This article provides a new and important piece to that puzzle and a better understanding of the abnormal degradation of BMPR-II that ultimately lead to a better understanding of the mechanisms behind PAH. The present article by Long et al provides encouraging data on chloroquine and hydroxychloroquine, and further studies will help enhance our understanding of the effects on the pulmonary circulation and the potential role in the treatment of patients with PAH.

Disclosures

None.

References


Key Words: Editorial ▪ autophagy ▪ pulmonary hypertension ▪ receptor
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Circ Res. 2013;112:1091-1093
doi: 10.1161/CIRCRESAHA.113.301247

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/112/8/1091

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