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Commentary

IL-33-HIF1α Axis in Hypoxic Pulmonary Hypertension

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Hypoxia-induced pulmonary hypertension (PH) is a leading cause of death, but despite its increasing morbidity and mortality no effective treatment has been discovered. Hypoxic PH is the outcome of a multi-step process involving epigenetic changes, cellular reprograming, proliferation, inflammation and vasoconstriction [1]. These pathological features ultimately lead to irreversible structural changes of the vasculature. Classical molecules that have been linked to these multiple pathologies include vascular endothelial growth factor (VEGF) and its receptors, and the hypoxia inducible factors (HIFs) 1α and 2α [2]. Simultaneously, recent progress in the field has unraveled the potential of cytokines related to Th1, Th2 and Th17 inflammation in driving multiple pathologies in preclinical models of PH [3–5]. Classically, hypoxia stabilizes HIF1α, leading to transcriptional regulation of many genes involved in hypoxic PH pathology including VEGF. Alternative, non-hypoxic regulators of HIF1α in hypoxic PH have not been clearly elucidated.

The study by Liu et al. in this issue of EBioMedicine [6] addresses this issue. By using *in vivo* studies in mice and *in vitro* experiments with human pulmonary artery endothelial and smooth muscle cells (HPAECs and HPASMCs), the authors report exciting data concerning the potential roles of an interleukin (IL)-33/ST2/HIF1α/VEGF signaling pathway in the pathogenesis of hypoxic PH. The authors report that hypoxia exposure upregulates the expression of IL-33/ST2 by PAECs, contributing to hypoxic pulmonary vascular remodeling *via* activating downstream HIF1α/VEGF signaling. They also report that HPAECs constitutively express IL-33 and its receptor ST2, and that hypoxia upregulates their expression. In addition, IL-33 acts on these cells to enhance proliferation, adhesion and angiogenesis in an ST2-dependent fashion. Liu et al. conclude that IL-33/ST2, operating through activation of the HIF1α/VEGF axis on PAECs, induces the angiogenesis and proliferation of PAECs, and may provide a basis for the initiation of PASMC remodeling which results in PH, with hypoxia a potential initiator for the proximate upregulation of the IL-33/ST2 axis.

The present work by Liu et al. complements prior reports on IL-33/ST2 in inflammation and remodeling processes [7–9], while supporting the clinical relevance of these findings by observing similar molecules upregulated in the structural endothelial cells of blood vessels of hypoxic patients. The requirement of ST2 receptor for the effect of HIF1α on VEGF as shown by Liu et al. is interesting and points to a novel insight into HIF1α regulation. Other studies showed HIF1α drives metabolic shift and VEGF controls proliferation and migration of endothelial cells [2]. Overall, Liu et al. convincingly prove their point by using multiple molecular biology approaches that IL-33 regulates HIF1α and VEGF.

Therefore, based on the current findings, what are the next steps towards the long term goal of developing effective treatments of hypoxic PH by targeting cytokines and its downstream signaling molecules? We suggest first reproducing and understanding the roles of IL-33 in the pathology of hypoxic PH, to permit more precise targeting of causal mechanisms. In particular, answering the following questions will be helpful:

1. Does IL-33 have a role in increasing vasoconstriction as well as fixed remodeling?
2. What are the critical mediators between hypoxia and IL-33 production?
3. Does the increase in IL-33 and ST2 by PAECs depend on or augment recruitment of bone marrow derived circulating cells? Monocytes also produce IL-33 [10], which may be promoted by similar or distinct pathways.
4. What will be the side effects of IL-33 blockade if it is targeted therapeutically?
5. Does IL-33 also regulate HIF2α in PAECs?

Despite these uncertainties, the current findings by Liu et al. support the possible therapeutic targeting of this pathway. One example of more selective targeting of pathologic hypoxic PH is an ongoing study of IL-6 receptor inhibition in PH (NCT02676947). In the future, targeting pathogenic cytokines could be an effective therapeutic approach to treat pulmonary vascular diseases such as hypoxic PH.

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