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RESEARCH HIGHLIGHT

Mutual inhibitory mechanisms between PPARγ and Hif-1α: implication in pulmonary hypertension

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Transcription factor hypoxia-inducible factor 1α (Hif-1α) is known for its crucial role in promoting the pathogenesis of pulmonary hypertension (PH). Previous studies have indicated the in-depth mechanisms that Hif-1α increases the distal pulmonary arterial (PA) pressure and vascular remodeling by triggering the intracellular calcium homeostasis, especially the store-operated calcium entry (SOCE) process. In our recent research paper published in the *Journal of Molecular Medicine*, we found that the transcription factor peroxisome proliferator-activated receptor γ (PPARγ) activation could attenuate the PH pathogenesis by suppressing the elevated distal PA pressure and vascular remodeling. Moreover, these effects are likely mediated through the inhibition of SOCE by suppressing Hif-1α. These results provided convincing evidence and novel mechanisms in supporting the protective roles of PPARγ on PH treatment. Then, by using comprehensive loss-of-function and gain-of-function strategies, we further identified the presence of a mutual inhibitory mechanism between PPARγ and Hif-1α. Basically, under chronic hypoxic stress, accumulated Hif-1α leads to abolished expression of PPARγ and progressive imbalance between PPARγ and Hif-1α, which promotes the PH progression; however, targeted PPARγ restoration approach reversely inhibits Hif-1α level and Hif-1α mediated signaling transduction, which subsequently attenuates the elevated pulmonary arterial pressure and vascular remodeling under PH pathogenesis.

Keywords: Pulmonary hypertension; PPARγ; Hif-1α; SOCE

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PPARγ inhibits pulmonary vascular remodeling by regulating intracellular calcium homeostasis in PASMCs

Peroxisome proliferator-activated receptors (PPARs), which are ubiquitously expressed in pulmonary vascular endothelial and smooth muscle cells [1, 2], are a group of ligand-activated nuclear hormone receptors superfamily with increasingly diverse functions as transcriptional regulators. There are three subtypes of PPARs: α, β/δ and γ [3]. PPARγ is originally known to participate in the processes of adipocyte differentiation and lipid metabolism [4]. However recently, accumulating evidences have indicated that decreases of PPARγ expression and function are associated with pulmonary hypertension (PH), while stimulating PPARγ acts a beneficial treatment for PH in experimental animal models [3, 5-8]. Similarly, in our recent published paper [9], we found that PPARγ agonist rosiglitazone significantly attenuated the elevated pulmonary arterial pressure and distal pulmonary arterial remodeling in both chronic hypoxia-induced pulmonary hypertension (CHPH) and monocrotaline-induced PH (MCT-PH) rats by rescuing hypoxia-downregulated PPARγ level. However interestingly, PPARγ agonist

rosiglitazone did not reverse the hypoxia-enhanced right ventricle hypertrophy, featured by the Fulton index (RV/LV+S). These results suggest a potential direct therapeutic role of PPARγ on the distal pulmonary vasculature, but not the heart. Moreover, in accompany with our previous study, PPARγ activation leads to attenuated hypoxia-elevated expression of store-operated calcium channels (SOCCs) component proteins canonical transient receptor potential 1 (TRPC1) and TRPC6, as well as hypoxia-triggered store operated calcium entry (SOCE) and baseline free intracellular calcium concentration ($[Ca^{2+}]_i$), which eventually caused suppressed proliferation of distal pulmonary arterial smooth muscle cells (PASMCs) and inhibited vascular thickening and remodeling of distal pulmonary arteries [9, 10].

Negative modulation of PPARγ on Hif-1α in CHPH and mutual inhibition between Hif-1α and PPARγ

Hypoxia inducible factor 1 (Hif-1) is a transcriptional activator that mediates gene expression changes by responding to cellular oxygen concentration changes [11, 12]. Hif-1 consists of two isoforms Hif-1α and Hif-1β, which functions by forming heterodimer. Hif-1β stably expresses under both normoxic and hypoxic conditions, while Hif-1α protein undergoes rapid degredation under normoxia but escapes oxygen dependent degradation and is stabilized under hypoxia. Thus, the activity of Hif-1 is dependent on Hif-1α [13, 14]. Previous studies have demonstrated that Hif-1α plays a crucial contributive role in PH by inducing the TRPC-SOCE-$[Ca^{2+}]_i$ signaling axis [15]. Moreover, the complicated regulative mechanism between PPARγ and Hif-1α in different cell and tissue types has been discussed in several previous studies. On one hand, PPARγ has been shown inhibited by Hif-1α activation upon hypoxic stress in the process of adipocyte differentiation [16]; while Hif-1α activation was also reported to upregulate PPARγ expression in cardiomyocytes in response to pathologic stress of cardiac metabolism [17]. On the other hand, PPARγ could act upstream and modulate the expression of Hif-1α in allergic airway disease of mice [18]. In our study, by using both loss-of-function and gain-of-function strategies, results showed that PPARγ activation could suppress Hif-1α, explaining that PPARγ attenuates the highlighted TRPC-SOCE-$[Ca^{2+}]_i$ signaling axis in hypoxic PASMCs by targeting to Hif-1α. Moreover, our results further demonstrated that PPARγ and Hif-1α share a mutual inhibitory regulation mechanism [9]. These results presented the first demonstration that PPARγ and Hif-1α share mutual inhibition and their relative imbalance leads to the pathogenesis of PH, while the PPARγ targeted rescue approach potentially reversed the PPARγ-Hif-1α imbalance and attenuated the disease development of PH.

PPARγ-Hif-1α counterbalance, new insights into pathogenesis or therapeutics of PH

Based on the finding of the mutual inhibitory mechanism between PPARγ and Hif-1α, our data presented more convincing evidence to prove the therapeutic effects of PPARγ on PH treatment and showed new insights into the roles and molecular mechanisms of PPARγ on PASMCs proliferation and PA remodeling under PH. Application of strategies to modulate the balance between PPARγ and Hif-1α might be useful novel approaches for the treatment of PH and worth further evaluation in the future study.

Conflicting interests

The authors have declared that no competing interests exist.

Acknowledgments

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