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Unveiling the lysosomal-cholesterol nexus: NCOA7's pivotal role in pulmonary artery hypertension pathogenesis and therapy

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Abstract

We read with great interest a recent study investigating the role of nuclear receptor coactivator 7 (NCOA7) as a critical regulator of lysosomal function, oxysterol, and bile acid metabolism, and its link to endothelial cells (ECs) inflammation and immune activation in pulmonary artery hypertension (PAH). The study demonstrated that NCOA7 deficiency exacerbated lysosomal dysfunction, leading to inflammatory sterol accumulation and immune activation, which subsequently triggers endothelial immune responses. Translationally, NCOA7 activation emerges as a promising therapeutic strategy, while plasma oxysterol and bile acid levels offer potential prognostic biomarkers for PAH severity and mortality.

PAH is a progressive disease marked by remodeling of distal pulmonary arteries, leading to elevated pulmonary vascular resistance (PVR), right ventricular (RV) failure, and ultimately death[1]. Inflammation and innate immunity are recognized as central to PAH pathogenesis[2]. Pulmonary vasculature in PAH recruits immune cells and exhibits elevated circulating levels of inflammatory cytokines and chemokines. Both immune cells and vascular cells, especially ECs, are important sources of these mediators, contributing to pathological vascular remodeling[3].

Lysosomes are critical organelles for degradation and recycling, requiring acidic pH maintained by the vacuolar H^+-ATPase (V-ATPase) for optimal enzymatic activity[4]. Dysregulated lysosomal acidification and impaired enzymatic function have been implicated in various inflammatory and autoimmune diseases[5,6]. Notably, lysosomal storage disorders (LSDs) have been observed in PAH patients, suggesting a potential link between lysosomal dysfunction and PAH pathophysiology[7]. NCOA7 regulates lysosomal acidification by interacting with the cytoplasmic domain of V-ATPase, modulating its assembly and function[8,9]. Given its regulatory role in lysosomal biology and emerging relevance to immune signaling, NCOA7 represents a compelling candidate for investigation in PAH.

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Harvey *et al.*'s study provides novel insights into the interplay between lysosomal biology, oxysterol/bile acid metabolism, and ECs inflammation in PAH[10]. Through integrative multi-omics and experimental approaches, the authors establish NCOA7 as a critical regulator of lysosomal function and sterol metabolism, offering new perspectives on PAH pathogenesis as well as potential diagnostic and therapeutic targets.

LYSOSOMAL DYSFUNCTION AND NCOA7 IN PAH

Lysosomes play a vital role in cholesterol degradation and recycling, with bile acids derived from cholesterol metabolism[11]. Harvey *et al.* investigated whether inflammation-induced ECs dysfunction alters lysosomal behavior[10]. Using unbiased transcriptomic analysis of pulmonary artery endothelial cells (PAECs) exposed to interleukin-1β (IL-1β), they identified significant upregulation of lysosomal regulatory genes, including NCOA7. These findings were further validated in PAH patients, interleukin-6 (*Il6)* transgenic mice models of pulmonary hypertension (PH), and cellular inflammatory models. Mechanistically, NCOA7 silencing in PAECs under proinflammatory conditions led to altered expression of genes involved in lysosomal acidification, particularly those encoding V-ATPase subunits. Among them, ATPase H^+ transporting V1 subunit B2 (ATP6V1B2) was significantly upregulated in ECs isolated from PAH patients and rodent PH models. NCOA7 was shown to directly interact with ATP6V1B2, enhancing its expression and facilitating V-ATPase assembly. Loss of NCOA7 impaired lysosomal acidification. This dysfunction manifested as lysosomal hypertrophy, lamellar inclusions, and intracellular sterol accumulation. These results confirm that NCOA7 is essential for V-ATPase function, and its deficiency contributes to lysosomal dysfunction in PAH.

INFLAMMATORY STEROL METABOLISM AND IMMUNE ACTIVATION

In PAECs, NCOA7 deficiency profoundly altered cholesterol biosynthesis pathways, reducing the expression of low-density lipoprotein receptor (LDLR) and impairing cholesterol uptake, resulting in intracellular cholesterol accumulation. In response, the expression of cholesterol 25-hydroxylase (CH25H), an oxysterol-generating enzyme, was significantly upregulated in NCOA7-deficient PAECs as well as in pulmonary endothelium from PAH patients and inflammatory rodent PH models. This upregulation led to increased production of oxysterols including 25-hydroxycholesterol (25HC), 27-hydroxycholesterol (27HC), and 7α-hydroxycholesterol, as well as downstream bile acid derivatives such as 7α-hydroxy-3-oxo-4-cholestenoic acid (7HOCA). Notably, these metabolites were also elevated in the plasma of PAH patients, correlating strongly with disease severity and mortality.

Moreover, NCOA7 deficiency promoted a proinflammatory endothelial phenotype, characterized by upregulation of vascular cell adhesion molecule-1 (VCAM1) and enhanced leukocyte adhesion. These effects were mediated via the NCOA7-cholesterol-oxysterol/bile acid axis. Functionally, NCOA7-deficient PAECs exhibited increased proliferation and resistance to apoptosis under proinflammatory conditions. Interestingly, CH25H inhibition reversed apoptosis resistance but paradoxically further enhanced cell proliferation, suggesting complex and context-dependent regulatory dynamics. The inconsistent effects of CH25H inhibition may stem from context-dependent differences in genetic models, cell types, and inflammatory states. In atherosclerosis, macrophage- or hematopoietic-specific Ch25h deficiency attenuates Toll-like receptor (TLR4)-p38 mitogen-activated protein kinase (p38 MAPK)-nuclear factor-κB (NF-κB) signaling, promotes cholesterol efflux and efferocytosis, and reduces apoptosis. By contrast, global CH25H deletion likely affects additional tissue-specific metabolic pathways, producing divergent outcomes[12]. These observations underscore the cell-specific role of CH25H in disease progression. These findings highlight essential requirement for further investigation, such as studies silencing CH25H in both basal and proinflammatory settings. Furthermore, treatment with bile acid derivatives such as 7HOCA markedly

amplified endothelial immune activation and leukocyte adhesion, underscoring the pathological contribution of inflammatory sterol metabolites in NCOA7-deficient PAECs.

VALIDATION *IN VIVO* AND CLINICAL RELEVANCE

To confirm these findings *in vivo*, Harvey *et al.* crossed *Il6* Tg^+ mice with *Ncoa7*$^{-/-}$ mice and exposed them to hypoxia to induce PH[10]. *Ncoa7*$^{-/-}$ mice exhibited exacerbated PH phenotypes, including elevated RV systolic pressure, PVR, and RV hypertrophy, accompanied by increased expression of VCAM1, CH25H, and enhanced monocyte infiltration. Plasma levels of oxysterols (e.g., 25HC, 7HOCA) were also significantly elevated, consistent with their association with PAH severity. Endothelial-specific *Ncoa7* inhibition using the 7C1 oligomeric lipid nanoparticle system, as well as orotracheal delivery of 7HOCA in *Il6* Tg^+ mice, further corroborated these findings. Both approaches worsened PH and amplified endothelial immune activation. Additional studies using conditional Ncoa7 knockout mice in various cell types, applied across different PH models, could help elucidate the underlying molecular mechanisms in greater detail.

Clinically, NCOA7-dependent oxysterols and bile acid metabolites were strongly associated with morbidity and mortality across large PAH patient cohorts (n = 2,756). Moreover, the authors identified an intronic SNP, rs11154337, located near a noncanonical promoter region of *NCOA7*. This variant regulates NCOA7 expression via RelA/p65 binding, as confirmed by chromatin conformation capture and chromatin immunoprecipitation assays in ECs. In CRISPR-Cas9-edited induced pluripotent stem cells-derived ECs (iPSC-ECs), the G allele increased NCOA7 and ATP6V1B2 expression, promoted lysosomal acidification, and reduced oxysterol/bile acid accumulation. These changes attenuated ECs immune activation, as evidenced by decreased VCAM1 expression and less leukocyte adhesion. Importantly, carriers of the G allele exhibited improved 6-minute walk distance (6MWD) and overall survival in both a discovery cohort (n = 93) and a validation cohort (n = 630), even after PVR adjustment, suggesting broader prognostic value.

THERAPEUTIC POTENTIAL OF TARGETING NCOA7

NCOA7 is proposed to function as a brake on inflammation and immune activation in PAECs of PAH. Its potential as a druggable target is critical for clinical translation in PAH treatment. In this study, Harvey *et al.* identified a small-molecule NCOA7 activator, compound 958, through structural modeling and virtual screening. This compound was optimized to 958ami by replacing an ester group with an amide moiety to enhance binding affinity to NCOA7[10]. In PAECs, 958ami promoted NCOA7-ATP6V1B2 interactions, restored lysosomal acidification, and downregulated CH25H/VCAM1 expression, thereby attenuating ECs immune activation. In the monocrotaline (MCT)-induced rat model of PH, 958ami significantly reduced CH25H and VCAM1 levels, decreased monocyte infiltration, and alleviated pulmonary vascular muscularization, RV hypertrophy, and RV systolic pressure without detectable toxicity. Compared with the MCT model, the Sugen5416-hypoxia (SuHx) rat model exhibits more chronic and sustained inflammation[13], representing another important preclinical PH model to evaluate the therapeutic effect of 958ami. Moreover, in clinical practice, combination therapy is commonly employed in patients with pulmonary arterial hypertension (PAH) to enhance therapeutic efficacy. Therefore, assessing the effects of 958ami in combination with currently approved PAH drugs in preclinical models will be critical to support its clinical translation as a disease-modifying therapy that could complement existing vasodilators or anti-proliferative treatments.

CRITICAL EVALUATION

Harvey *et al.*'s study is a landmark contribution, connecting NCOA7 to lysosomal function, cholesterol metabolism, and PAECs inflammation in PAH through robust genetic, cellular, and animal studies[10]. The identification of SNP rs11154337, oxysterol/bile acid biomarkers, and the NCOA7 activator 958ami offers

significant translational potential for both diagnostics and targeted therapies. However, the mechanistic interplay between IL-1β, V-ATPase activation, and lysosomal acidification is complex. As a proinflammatory cytokine, IL-1β upregulates NCOA7 and V-ATPase subunits (ATPase H^+ transporting V1 subunit B2, ATP6V1B2) in PAECs, enhancing lysosomal acidification to clear cholesterol and prevent oxysterol accumulation-driven inflammation. This response appears initially beneficial and may represent an adaptive attempt to mitigate inflammatory stress. Yet in chronic PAH, where inflammatory stress persists, this endogenous induction of NCOA7 appears insufficient to maintain lysosomal homeostasis, ultimately contributing to dysfunction and pathological progression. Paradoxically, NCOA7 overexpression (via the G allele of SNP rs11154337, pharmacological activation with 958ami, or strong inflammation) is protective. Specifically, enhanced NCOA7 expression amplifies this compensatory mechanism by strengthening NCOA7-ATP6V1B2 interactions, restoring lysosomal function, and reducing inflammation through the NCOA7-V-ATPase axis. This highlights NCOA7's efficacy depends on expression levels, with physiological induction inadequate in chronic disease but deliberate overexpression overcoming these limitations.

One potential biological explanation for the *"paradoxical"* functions of NCOA7 is a threshold-dependent protective response. During acute or moderate inflammatory stress, endogenous upregulation of NCOA7 may act as an adaptive mechanism, enhancing lysosomal acidification and promoting sterol clearance to maintain cellular homeostasis. In contrast, under chronic inflammatory conditions, such as during the development of PAH, persistent inflammatory and metabolic stress may overwhelm this compensatory response. As a result, physiological induction of NCOA7 may no longer be sufficient to sustain lysosomal function. Consequently, robust enhancement of NCOA7 activity, either through genetic variants or pharmacological manipulation, may be required to restore lysosomal homeostasis and suppress downstream immune pathway activation. Alternatively, chronic inflammation may impair NCOA7 function through unknown mechanisms, such as post-translational modifications or alterations in V-ATPase assembly, thereby diminishing its protective capacity. In such settings, strategies aimed at achieving higher levels or sustained activation of the NCOA7-V-ATPase axis may be necessary to confer effective protection. Further studies should delineate why endogenous NCOA7 induction falters in chronic disease and define the expression threshold required for protective effects. It is critical to evaluate NCOA7 expression profiles during the onset, progression, and regression of PAH to determine the optimal stage for targeting NCOA7 therapeutically. Beyond a simple threshold-dependent response, an alternative explanation is that chronic inflammatory stress may compromise NCOA7 function despite its transcriptional upregulation. Sustained oxidative or nitrosative stress, which has been reported in inflammatory and vascular remodeling contexts of PAH[14], might potentially induce post-translational modifications of NCOA7, such as nitration or aberrant phosphorylation. These modifications might interfere with its interaction with the V-ATPase complex. Impaired NCOA7-V-ATPase coupling would, in turn, limit lysosomal acidification. Under such conditions, transcriptional induction alone may be insufficient, raising the possibility that future pharmacological strategies aimed at enhancing NCOA7 expression or activity could be required to overcome both quantitative insufficiency and qualitative dysfunction.

Moreover, the study's exclusive focus on ECs overlooks NCOA7's role in pulmonary artery smooth muscle cells (PASMCs), despite immunofluorescence evidence of its expression in the SMC layer of remodeled vessels. Given the central contribution of PASMCs proliferation, migration, and phenotypic switching to pulmonary vascular remodeling, it will be necessary to investigate whether NCOA7 exerts cell-autonomous effects in PASMCs through in vitro molecular mechanisms and *in vivo* PH therapeutic effect analogous to those described in endothelial cells, such as lysosomal regulation of cholesterol handling and immune-metabolic reprogramming. Therefore, the generation of smooth muscle cell-specific NCOA7 knockout mice and targeted manipulation of NCOA7 in PASMCs in PH settings will clarify whether NCOA7 activation confers vessel-wide protection or primarily modulates endothelial-driven inflammatory signaling.

The study's focus on inflammatory PH models (*Il6* transgenic, MCT (monocrotaline) models) limits insights into distinct PH subtypes regarding the generalizability of the NCOA7-lysosomal axis. Notably, immune-mediated forms of PH-such as PAH associated with systemic autoimmune diseases including SLE (systemic lupus erythematosus) or RA (rheumatoid arthritis)-are characterized by chronic immune activation (interferon signaling), sustained oxidative stress, and immune-metabolic imbalance. In these pathological contexts, NCOA7 is robustly induced yet functionally insufficient, suggesting that dysregulation of the NCOA7-lysosomal axis may contribute to immune-driven PAH. This observation raises the possibility that distinct immune-metabolic phenotypes, defined by lysosomal competence or oxysterol signatures, may exist within PAH. It also highlights a rationale for future studies evaluating combination strategies that incorporate immunosuppressive therapies with conventional PAH vasodilators in SLE-PAH or RA-PAH.

Another unresolved issue concerns the inconsistent effects of cholesterol 25-hydroxylase (CH25H) inhibition, which attenuates apoptosis resistance while paradoxically enhancing cellular proliferation across different experimental systems. Rather than reflecting simple context dependency, these divergent phenotypes likely arise from fundamental differences in how distinct vascular cell types utilize sterol metabolism. In endothelial and immune-associated cell populations, existing studies suggest that CH25H-derived oxysterols predominantly intersect with inflammatory signaling and cell survival pathways[15]. By contrast, in highly proliferative cell types such as pulmonary artery smooth muscle cells (PASMCs) - where metabolic reprogramming, mitochondrial bioenergetics, and cell cycle control are central pathological features[16] - alterations in sterol flux may influence mitochondrial function or checkpoint regulation, thereby producing distinct biological consequences. Importantly, these interpretations remain speculative and underscore the need for future cell type-specific studies to delineate how CH25H and oxysterol metabolism differentially shape inflammatory versus proliferative responses in PAH, which will be critical for predicting therapeutic responses to interventions targeting sterol metabolism.

From a translational perspective, the identification of 958ami as a small-molecule activator of NCOA7 provides proof of concept that targeting lysosomal-immune coupling may confer disease-modifying potential in PAH. While efficacy in the monocrotaline model supports its anti-inflammatory and anti-remodeling effects, validation in the Sugen5416-hypoxia (SuHx) model represents a critical next step, particularly with parallel assessment of right ventricular (RV) structure and function, given the central role of RV failure in determining clinical outcomes in PAH. In addition, extension of these findings to more diverse patient populations beyond predominantly European cohorts, together with rigorous evaluation of long-term safety, will be essential for clinical translation. Moreover, as PAH therapy is inherently combinatorial, preclinical evaluation of 958ami alongside established vasodilators - such as endothelin receptor antagonists or soluble guanylate cyclase stimulators - will be important to determine whether complementary targeting of immune-metabolic drivers and vascular dysfunction can enhance therapeutic efficacy.

Beyond their mechanistic implications, dysregulated oxysterol and bile acid metabolism downstream of the NCOA7-lysosomal axis raises the possibility of developing mechanism-informed circulating biomarkers in PAH. Future large-scale, metabolomics-integrated clinical studies will be required to determine whether pulmonary-derived oxysterol and bile acid signatures can capture disease severity, refine risk stratification beyond existing clinical tools, and serve as dynamic pharmacodynamic readouts for therapies targeting immune-metabolic and lysosomal pathways, including NCOA7-directed interventions.

In summary, Harvey *et al.*'s study reshapes the landscape of PAH research by establishing a novel lysosomal-cholesterol-immune axis centered on NCOA7[10]. The SNP rs11154337 boosts NCOA7 expression, improving survival, while oxysterol/bile acid biomarkers and the NCOA7 activator 958ami pave the way for personalized diagnostics and therapies. Future studies should prioritize elucidating NCOA7 expression dynamics across the PAH stage, exploring the role of NCOA7 in PASMCs, and RV failure models, extending validation to non-inflammatory PH models, and assess the safety and efficacy of 958ami in diverse populations to fully enhance its translational potential.

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Authors' contributions

Wrote the original draft: Li Y
Revised and reviewed this work: Liu SF, Deng L

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Not applicable.

AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tool ChatGPT (OpenAI, GPT-5 series, accessed before 2026-03-03) was used solely for language editing. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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