HCKing COPD: unveiling the role of HCK in COPD pathogenesis

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eBioMedicine
2025;115: 105714
Published Online xxx
https://doi.org/10.1016/j.ebiom.2025.105714

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease of the lungs that imparts a significant global disease burden, affects >400 million individuals, and causes >3 million deaths annually.[1] The disease is characterised by a progressive decline in lung function, chronic persistent cough, and shortness of breath (dyspnoea) that are underpinned by intractable inflammation as well as remodelling events, including alveolar tissue destruction that causes emphysema, and mucus hypersecretion.[2] Patients with COPD also have an increased risk for developing lung infections. Current treatments aim to alleviate disease symptoms and include bronchodilators that dilate the airways to improve airflow, and anti-inflammatory corticosteroids that have limited efficacy for suppressing disease-associated lung inflammation. Importantly, these treatments are not cures and do not halt disease progression.

There remains a critical shortfall of transformative therapeutic advances for COPD despite extensive research efforts to define the repertoire of pathogenic mechanisms that drive disease development and progression. Recent research efforts towards developing biological agents that aim to control the intractable inflammation by targeting single cytokines[3] or their receptors[4] show that this approach, even with carefully selected cohorts, are not efficacious for all patients with COPD and are not curative. Looking forward, understanding the interrelationship between different disease drivers may be key to developing treatments that can temper multiple disease processes simultaneously.

In the May issue of *eBioMedicine*, Hsu and colleagues report their findings from a series of elegant experiments in mice that demonstrate pathogenic roles for augmented haematopoietic cell kinase (HCK) responses in COPD.[5] HCK is a member of the SRC family of cytoplasmic tyrosine kinases, plays key regulatory roles in myeloid cell activity, and is expressed in cells of the myeloid and B cell lineages. Interestingly, gain-of-function polymorphisms in *HCK* and increased HCK activity are prominently featured in COPD. A recent case study of a patient with a *de novo* mutation in HCK leading to loss of the inhibitory tyrosine (Tyr)522 caused myeloid cell activation and pulmonary inflammation that was poorly responsive to steroids and immunotherapy.[6] Furthermore, overactivation of the Hck enzyme in mice ($Hck^{F/F}$) produces features of COPD, including mucus production, inflammation, and emphysema-like alveolar enlargement.[7] Therefore, increasing knowledge of how Hck operates in COPD and developing nuanced approaches towards suppressing excessive/uncontrolled Hck may yield multifaceted benefits that can more effectively treat a wide range of patients with COPD.

The authors demonstrate that G-CSF produced by non-haematopoietic cells is responsible for $Hck^{F/F}$ cell recruitment into the lungs, leading to inflammation and emphysema. They also show that $Csf^{-/-}$ recipients, compared to wild type recipients, have blunted IL-17A responses following replenishment with $Hck^{F/F}$ cells. Interestingly, this effect was associated with protection against emphysematous destruction but not $Hck^{F/F}$ cell-induced goblet cell hyperplasia. It is also possible that immune factors such as CCL5/RANTES contribute to the pulmonary inflammation observed in $Hck^{F/F}$ mice. Whilst these data are informative, they suggest that there are still undiscovered links between G-CSF, IL-17A, and mucus secreting cell hyperplasia in this system. Importantly, these data show that mucus secreting cell hyperplasia and emphysema have distinct, but Hck-dependent, pathological aetiologies. The authors also show that γδ T cells are abundant in the airways of $Hck^{F/F}$ mice, have an effector-memory phenotype, and are skewed towards IL-17A production. Depletion of γδ T cells ($Tcrd^{-/-}$ mice) also induced the expansion of MAIT cells, which was further increased in $Hck^{F/F}Tcrd^{-/-}$ mice.

The studies detailed in this manuscript are convincing and intriguing, however, there remains questions to be answered. For example, whether intraperitoneal administration of dexamethasone adequately tests steroid sensitivity in the lungs in experimental COPD should be confirmed through comparative examination against intranasal delivery. Furthermore, investigations into the contributions of pro-resolving and/or anti-protease factors in disease pathogenesis in $Hck^{F/F}$ mice would be informative. This model is also ideal for interrogating pathogenic effects of infectious or environmental stimuli.

Unlike many other kinases, HCK can be inhibited using a small molecule, such as RK-20449, which has been shown to efficaciously reduce leukaemia stem cell burden in a mouse model of highly aggressive therapy-resistant acute myeloid leukaemia.[8] Assessments of HCK-targeting interventions in this model may uncover

DOI of original article: https://doi.org/10.1016/j.ebiom.2025.105707
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new functions of HCK and demonstrate the potential for therapeutic targeting of this factor in COPD. These exciting studies by Hsu and colleagues highlight a clear rationale for targeting HCK to ameliorate COPD and pre-COPD.

Contributors

RYK: Conceptualisation, Writing—original draft, Writing—review & editing.

CD: Conceptualisation, Writing—original draft, Writing—review & editing.

Declaration of interests

The authors assert that they are not aware of any conflict of interest that would affect this manuscript.

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