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LETTER

A humanized mouse model to study asthmatic airway remodeling and Muc-5ac secretion via the human IL-33

To the Editor,

Numerous signaling pathways and treatment strategies have been discovered in the study of asthma, but effective animal models for the preclinical validation of efficacy and safety are lacking.[1] Reconstructing humanized mice with a human immune system is essential to the simulation of human asthma, will help accelerate research on the pathogenesis of asthma, and is crucial for novel treatments.[2] NOG-EXL [the formal name, is NOD.Cg-Prkdc^{scid}IL2rg^{tm1Sug}Tg(SV40/HTLV-IL3, CSF2)10-7Jic/JicCrl] mice are constructed by transferring human interleukin (IL)-3 and the granulocyte–macrophage colony-stimulating factor on the basis of NOG (the formal name, is NOD.Cg-Prkdc^{scid}IL2rg^{tm1Sug}/JicCrl). Human cord blood-derived hematopoietic stem cells (huCD34+HSC) transplanted into NOG-EXL mice, namely, huHSC-NOG-EXL mice, show an immune system that includes human myeloid cells–granulocytes, dendritic cells, mast cells, eosinophils, monocytes, macrophages, B cells, and T cells–differentiated and mature.[3,4] In general, the rationale of the huHSC-NOG-EXL mice model for studying asthma is unclear. Previous studies reported that IL-33 can function as an alarm signal in asthma.[5,6] Therefore, this study constructed a humanized asthma mice using huHSC-NOG-EXL mice induced by the human IL-33 (hIL-33) to study asthmatic airway remodeling and mucous secretion.

Laboratory routinely engrafts 25,000 huCD34+ cells into irradiated NOG-EXL mice. Flow cytometry results show that the proportion of human CD45 in huHSC-NOG-EXL mice was greater than 50% (Figure 1A). The huHSC-NOG-EXL mice were intranasally administrated with 2 μg/10 μL of hIL-33 or 10 μL of saline for 4 consecutive days (Figure 1B). Human mast and T cells infiltrated the lung airway in huHSC-NOG-EXL mice through the treatment with hIL-33 compared with the saline group (Figure 1C–F). The human IL-5 and IL-13 of the bronchoalveolar lavage fluid also significantly increased in hIL-33-induced huHSC-NOG-EXL mice (Figure 1G,H). Then, we performed mRNA transcriptome analysis on hIL-33-induced huHSC-NOG-EXL mice. The criteria for screening the differentially expressed human genes are $p < .05$ and cut-off fold change >2. We found that 83 genes were significantly upregulated, and 43 genes were significantly downregulated (Figure 1I,J). The GO and KEGG enrichment pathways based on the background of the upregulated human genes showed that the upregulated human genes are closely associated with eosinophilic asthma (Figure 1K,L).

Next, the pathological correlation staining was assessed. HE staining showed inflammatory cell infiltration in hIL-33-induced huHSC-NOG-EXL mice (Figure 2A,E). Masson staining showed considerable collagen deposition around the airway in hIL-33-induced huHSC-NOG-EXL mice (Figure 2B,F). PAS and Muc-5ac staining demonstrated that the mucous secretion remarkably increased on the airway epithelium of hIL-33-induced huHSC-NOG-EXL mice (Figure 2C,D,G,H). However, the Muc-5b secretion did not increase on the airway epithelium of hIL-33-induced huHSC-NOG-EXL mice (this data are not shown).

In conclusion, this humanized mouse model is valuable in clinical strategies for asthma study.

FUNDING INFORMATION

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AUTHOR CONTRIBUTIONS

Dong Zhang and Liang Dong conceived and conducted the study, wrote the original draft, interpreted the data, and proofread the manuscript. Jintao Zhang, Changjuan Xu, Qian Qi, and Rong Zeng supervised the data analysis, and drafted some parts of the initial figures. Dong Zhang, Xiaofei Liu, Yun Pan, and Jiawei Xu raised the mice and analyzed the data. All authors approved the publication of the manuscript.

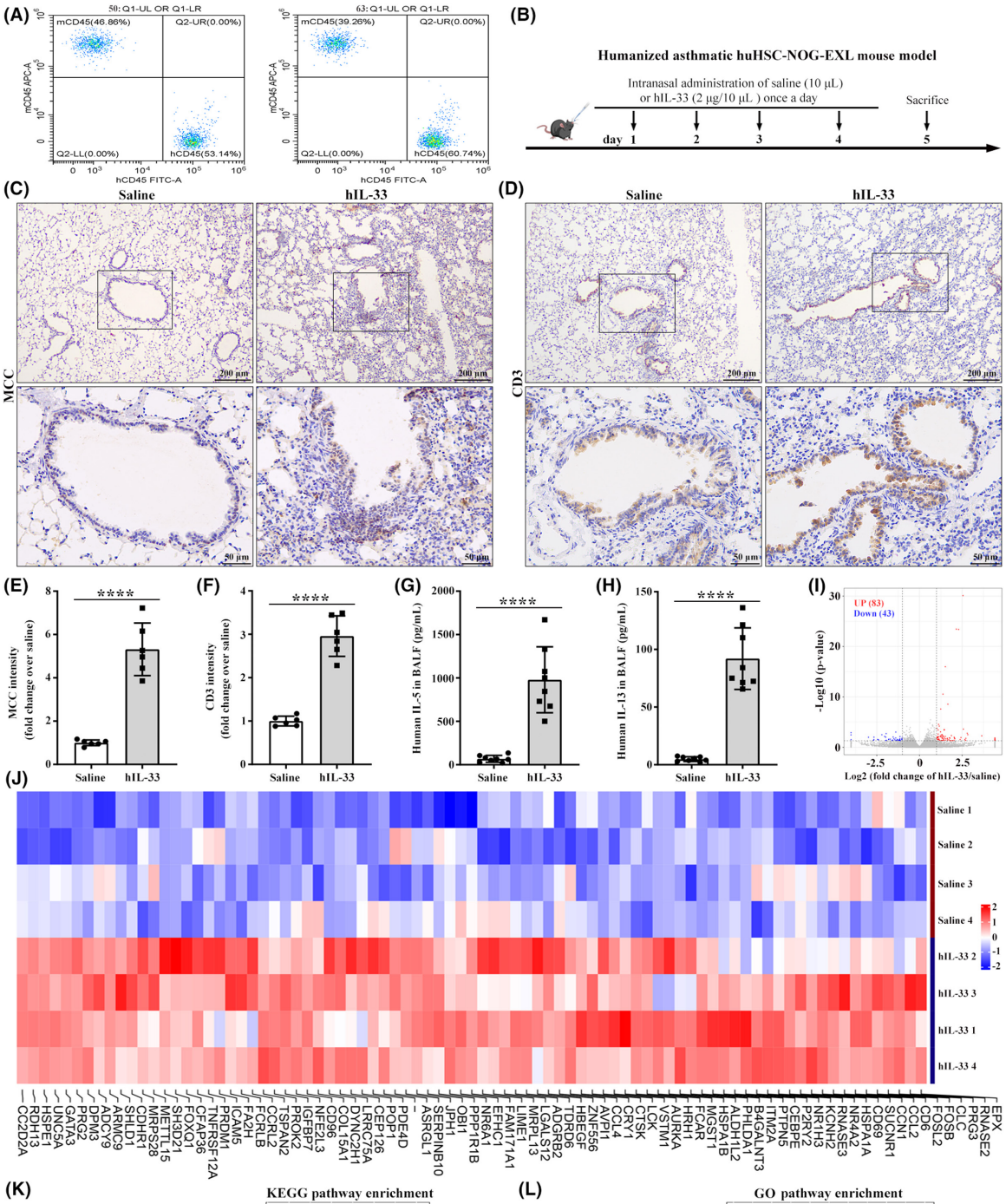

FIGURE 1 hIL-33-induced humanized asthmatic huHSC-NOG-EXL mouse model ($n = 6$). (A) Assessment of human CD45+ cells by flow cytometry for 7 weeks in the peripheral blood of human cord blood-derived hematopoietic stem cells (HSC)-reconstituted NOG-EXL mice. (B) Strategy for hIL-33-induced humanized asthmatic model. (C, D) The immunostaining analysis of the mast cell chymase (MCC) and CD3 in mouse lungs was used in assessing human mast and CD3+ T cells. Magnification 40×, scale bar: 200 μm; magnification 200×, scale bar: 50 μm. (E, F) Intensity analysis of (C) and (D). (G, H) The human IL-5 and IL-13 levels in the bronchoalveolar lavage fluid (BALF). Analysis of differentially expressed human gene in hIL-33 compared with the saline group. (I) The volcano plot exhibits the differentially expressed human genes between groups. (J) The heatmap shows the up-regulated 83 human genes between groups. (K) The chart illustrates the KEGG enrichment pathways based on upregulated human genes. (L) The chart illustrates the GO enrichment pathways based on upregulated human genes. Data are expressed as the means ± SD of six independent experiments. ****$p < .0001$.

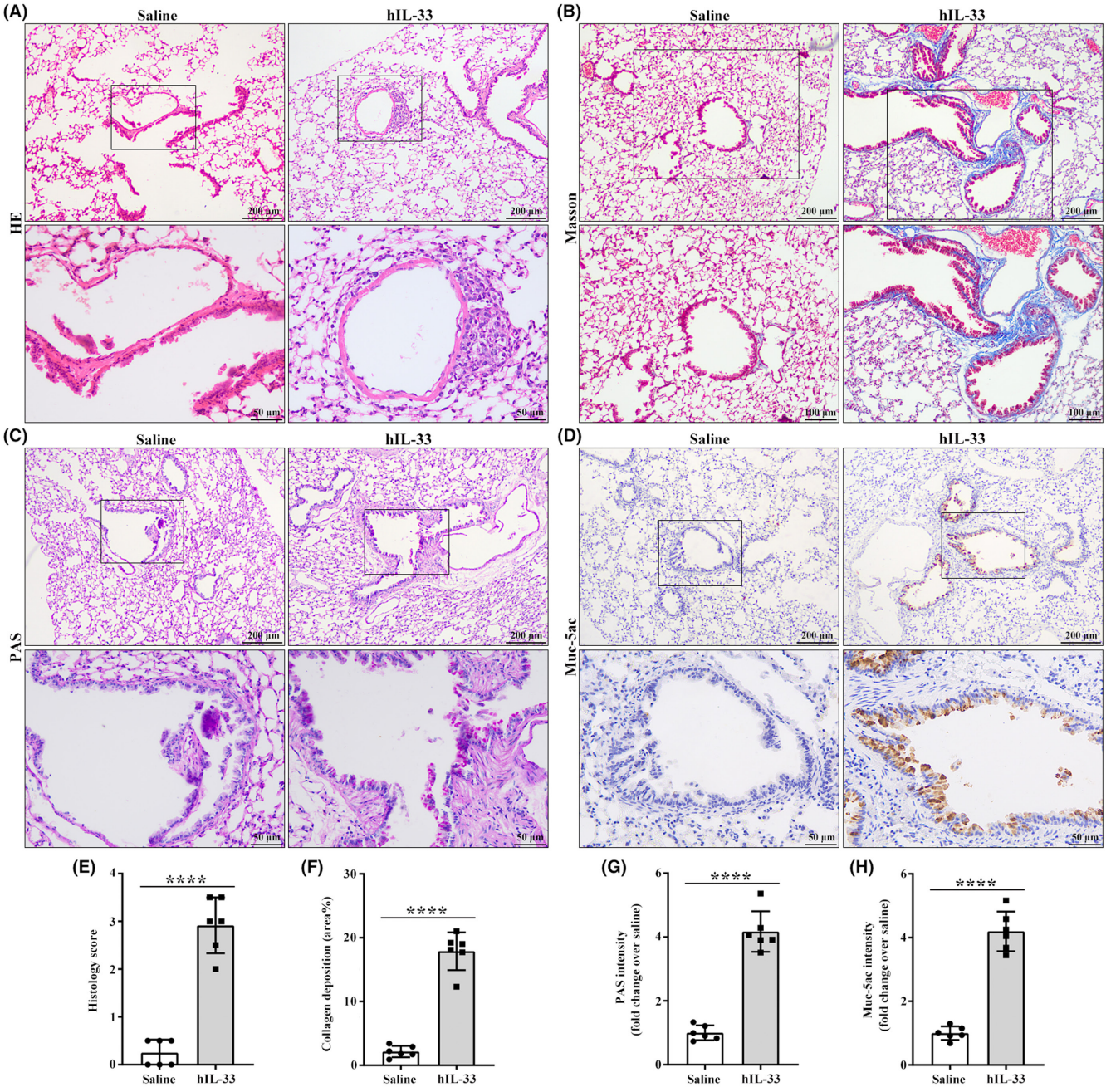

FIGURE 2 Pathological correlation staining in hIL-33-induced humanized asthmatic huHSC NOG-EXL mice ($n = 6$). (A) HE, (B) Masson, (C) PAS, and (D) Muc-5ac in mouse lungs of huHSC-NOG-EXL. (E-H) Intensity analysis of (A–D). Magnification 40×, scale bar: 200 μm; magnification 100×, scale bar: 100 μm; magnification 200×, scale bar: 50 μm. Data are expressed as the means ± SD of six independent experiments. ****$p < .0001$.

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CONFLICT OF INTEREST STATEMENT

All authors have no conflict of interest and nothing to disclose.

DATA AVAILABILITY STATEMENT

These sequence data have been submitted to the GenBank databases under accession number PRJNA1048633. Materials and methods in this study were provided by Supplementary Data—Materials and Methods. The other data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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