

Highlight: comparative single-cell analysis reveals how birds and mammals build distinct lung architectures

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Endothermic vertebrates—birds and mammals—have convergently evolved specialized respiratory systems that can sustain high metabolic rates. But while both avian and mammalian lungs have evolved for efficient gas exchange, each lineage's respiratory system has acquired highly specialized adaptations. Birds have developed a rigid, tubular air-capillary network that enables continuous, unidirectional gas exchange made possible by a clear anatomical division. As such, fresh and deoxygenated air do not mix, as inhalation and exhalation follow different routes. Mammals, on the other hand, have compliant, sac-like alveoli lungs that operate via tidal ventilation, in which air flows in and out along the same bronchial pathways.

While these anatomical differences are well documented, the cellular and molecular mechanisms underlying the development and evolutionary divergence of these two distinct types of lung architecture remain poorly understood. To bridge this gap, a research team led by Yanhua Qu from the Institute of Zoology at the Chinese Academy of Sciences characterized these differences at unprecedented cellular resolution, in a study now published in *Molecular Biology and Evolution* (Hao et al. 2026). The central questions the team asked were, according to Qu, “what are the cellular and molecular features that distinguish the avian lung from the mammalian lung, and how do these differences arise across development?”

Hao et al. (2026) began their study by generating the first single-cell transcriptomic atlas of the lung spanning developmental stages in a wild bird, the Eurasian tree sparrow (*Passer montanus*; Fig. 1). The authors generated data from lung tissues of six neonatal and seven adult tree sparrows. Developing this resource was an essential starting point, since previously generated avian lung single-cell data focused on domestic species and only adult individuals (Chen et al. 2021). With their expansive dataset, the authors identified 17 unique cell types, including homologs of the widely recognized alveolar type I (AT1) and type II (AT2) cells of mammals, as well as a distinct cluster of hybrid “AT1/AT2” cells.

To investigate how the development of these and other lung cell types differs between birds and mammals, the authors compared the transcriptional profiles of the tree sparrow samples to

previously published single-cell lung data from mice and humans. They found the greatest transcriptional divergence between the AT1 and AT2 cells, which is likely explained by their functional significance in the context of each lineage's respiratory evolution. Avian AT1 cells form rigid capillary walls for unidirectional airflow, whereas mammalian AT1 cells line pliable alveoli that require expansion and recoil. Likewise, avian AT2 cells produce surfactant adapted to maintain airflow in tubes, whereas mammalian surfactant prevents alveolar collapse. This finding, combined with the enrichment of conserved developmental pathways, illustrates a key evolutionary principle: “shared molecular toolkits are deployed in different spatio-temporal patterns and with different transcriptional outputs to generate distinct structural outcomes,” according to Qu.

When comparing neonatal and adult lung transcriptomes in the tree sparrow, Hao et al. (2026) revealed conservation of cell types alongside significant shifts in their proportions across developmental stages. For example, the neonatal lung contains higher fractions of structural cell types, reflecting lung maturation during development, while adult lungs have an increased proportion of cells that support adaptive immune responses. Most importantly, the authors observed persistence of the hybrid “AT1/AT2” cells into adulthood, a feature lost postnatally in mammals. “This persistence suggests avian lungs maintain developmental plasticity for longer, allowing extended morphogenesis of the complex tubular network,” according to Qu, highlighting a key innovation in avian lung development.

Concurrently with its central role in respiration, the lung serves as a primary target tissue for respiratory viruses, with cellular diversity playing a major role in determining host susceptibility (Clementi et al. 2021). To understand if viral susceptibility differs between avian and mammalian lung cells, Hao et al. (2026) analyzed the expression of 18 viral receptor genes in tree sparrows, mice, and humans. As viral entry depends on these receptors, their expression points to potential susceptibility, while their absence indicates likely resistance. Among the most important findings, the authors revealed that the entry receptor for influenza A is conserved and broadly expressed across all major cell

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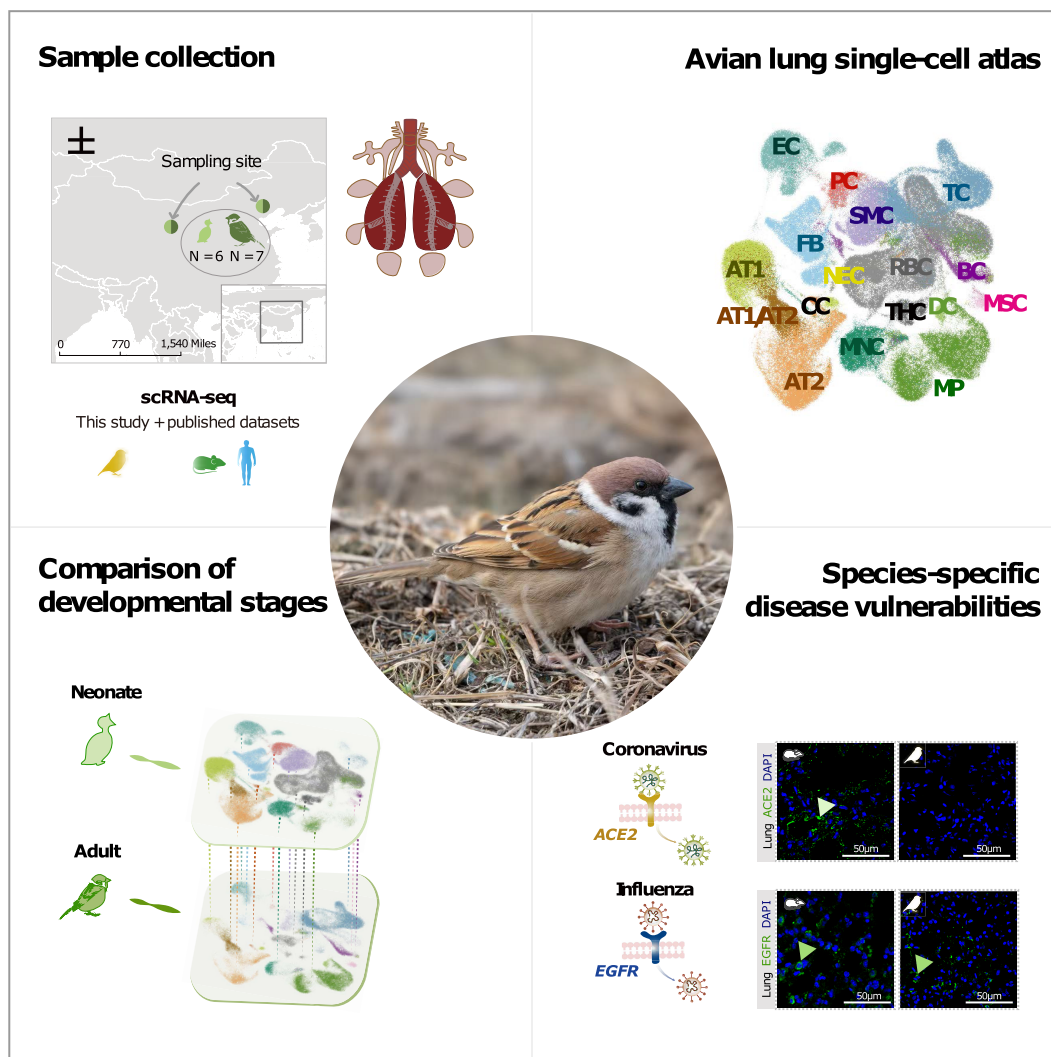


Figure 1 Single-cell comparison of the avian compared to mammalian lung across developmental stages. The Eurasian tree sparrow (*P. montanus*) (shown in the center), a common passerine that is present across the Palearctic realm, was used to create the first single-cell atlas of a wild avian lung. Samples were collected from six neonatal and seven adult individuals and compared with previously published mouse and human datasets (top left). Among the 17 cell types identified in the sparrow lung (top right), the alveolar types AT1, AT2, and AT1/AT2 show the greatest transcriptional divergence across species, highlighting their role in their diverse lung structure. Comparison of neonatal and adult lung atlases (bottom left) reveals a shift in cell proportions from structural development to immune functions with maturation; notably, the AT1/AT2 hybrid cell type persists in adult avian lung but is lost in adult mammals, suggesting maintenance of developmental plasticity of the bird lung. Finally, analysis of species-specific susceptibility shows that only mammals express the viral receptor for SARS-CoV-2, explaining avian resistance, while both taxa express receptors for influenza viruses, indicating their shared vulnerability (bottom right).

types in both birds and mammals. According to Qu, “this conserved expression pattern explains the wide host range of influenza viruses and suggests that birds may serve as reservoirs for influenza strains,” highlighting this study’s important implications for human and wildlife health (Peacock et al. 2025).

On the other hand, the authors also found that other receptors show marked species-specific divergence. In particular, they found that ACE2, the primary receptor for SARS-CoV-2 in mammalian lung cells, is not expressed in tree sparrows, providing a molecular explanation for the observed resistance of birds to SARS-CoV-2. Yanhua Qu highlights that these results “underscore the importance of integrating both cellular and anatomical perspectives when assessing zoonotic risk and informing pandemic preparedness.”

This study opens up new avenues for understanding evolutionary novelty and demonstrates how single-cell transcriptomics

can shed light on how structural and functional differences arise from underlying molecular and cellular mechanisms. According to Qu, “the avian lung is not merely an evolutionary curiosity, but a powerful and underappreciated model for addressing fundamental questions in regeneration, high-performance physiology, and host-pathogen interactions—insights that extend far beyond bird biology and into core principles of human biology and disease.”

Want to learn more? Check out these other articles on single-cell studies recently published in *SMBE* journals:

- Shi-Xin Wu, Guo-Wen Wang, Rui-Dong Wan, Rong-Ge Yan, Xue Gao, Rui-Na Zhang, Qi-Lin Yang, You-Gui Fang, Gong-Xue Jia, Qi-En Yang, Dynamic regulation of spermatogenesis and hybrid sterility revealed by single-cell analysis in yak and cattle,

Molecular Biology and Evolution, Volume 43, Issue 2, February 2026, msag027, <https://doi.org/10.1093/molbev/msag027>.

- Aundrea K Westfall, Siddharth S Gopalan, Blair W Perry, Richard H Adams, Anthony J Saviola, Stephen P Mackessy, Todd A Castoe, Single-cell heterogeneity in snake venom expression is hardwired by co-option of regulators from progressively activated pathways, *Genome Biology and Evolution*, Volume 15, Issue 6, June 2023, evad109, <https://doi.org/10.1093/gbe/evad109>.
- Roy Levinger, Dafna Tussia-Cohen, Sivan Friedman, Yan Lender, Yomiran Nissan, Evgeny Fraimovitch, Yuval Gavriel, Jacqueline L E Tearle, Aleksandra A Kolodziejczyk, Kyung-Mee Moon, Tomás Gomes, Natalia Kunowska, Maya Weinberg, Giacomo Donati, Leonard J Foster, Kylie R James, Yossi Yovel, Tzachi Hagai, Single-cell and spatial transcriptomics illuminate bat immunity and barrier tissue evolution, *Molecular Biology and Evolution*, Volume 42, Issue 2, February 2025, msaf017, <https://doi.org/10.1093/molbev/msaf017>.
- Elizabeth C Cooney, Noriko Okamoto, Anna Cho, Elisabeth Hehenberger, Thomas A Richards, Alyson E Santoro, Alexandra Z Worden, Brian S Leander, Patrick J Keeling, Single-cell transcriptomics of abedinium reveals a new early-branching dinoflagellate lineage, *Genome Biology and Evolution*, Volume 12, Issue 12, December 2020, Pages 2417 to 2428, <https://doi.org/10.1093/gbe/evaa196>.

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