Normal lung development needs self-eating

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Autophagy is a Greek-derived concept that means "self-eating" and is increasingly recognized as an important regulator of homeostasis and disease. In this issue of the *JCI*, Yeganeh et al. report the important finding that intrinsic autophagy is required for normal progression of lung development. Conditional deletion of the beclin 1–encoding gene (*Becn1*) specifically within lung epithelial cells of embryonic mice resulted in neonatal lethal respiratory distress that was associated with negative impacts on airway branching and differentiation of airway epithelial cell lineages. The authors draw speculative parallels with the alveolar simplification phenotype of bronchopulmonary dysplasia in premature human infants and suggest that stimulation of autophagy by AMP-dependent kinase activation might conceivably rescue these phenotypes.

Autophagy in the lung

Autophagy is a Greek-derived neologism meaning "self-eating." It is a normal physiological process by which cells and their constituent organelles can be eliminated and recycled during states of cellular stress, such as starvation. Over the previous decade, there has been a surge of interest in autophagy, as both a cell and organism survival mechanism during starvation as well as a potential therapeutic target in various human diseases, including cancer and fibrosis. Since 2010, research into the role of autophagy in the lung has dramatically increased and focused on diverse areas, including chronic respiratory disease, fibrosis, lung cancer, inflammation-mediated injury, and emphysema (1–15). Now, Yeganeh and colleagues (16) provide compelling evidence that intrinsic autophagy is required for normal progression of lung development. Early abrogation of autophagy via conditional deletion of beclin 1 (*Becn1*), which regulates autophagy-programmed cell death via interactions with BCL-2 or PI3K, specifically within lung epithelial cells resulted in neonatal lethal respiratory distress. Induction of lung epithelium–specific *Becn1* knockout at an early time point in gestation (E10.5) reduced airway branching and saccule formation and failed to optimally thin the lung mesenchyme. Animals in which the same deletion was induced at a later time point in gestation (E16.5) presented with reduced terminal air sac formation and vascularization. An important caveat to note about these experiments is that the double-transgenic approach used in this study [*Becn1*$^{fl/fl}$ mice crossed with *Sftpc-rtTA tet(o)Cre* mice] is notoriously inefficient for gene deletion; therefore, induction of *Becn1* knockout at later stages could possibly be even more penetrant and severe if a stronger driver, such as sonic hedgehog–*Cre*, were used for these experiments.

Conclusions and future considerations

Yeganeh et al. nevertheless draw potentially insightful parallels between their observations in mice and the alveolar simplification that is characteristic of bronchopulmonary dysplasia (BPD) in premature human infants (16). This is an intriguing speculation that could perhaps be of clinical relevance, as BPD is characterized by some of the defects, including altered saccule formation, airway branching, and mesenchymal thinning, that were observed in the mouse model. What makes the lung mesenchyme thin out during the latter part of gestation and how this continues postnatally into the alveolar phase of lung development have been something of a mystery. Apoptosis, particularly in the mesenchyme, is present, but has not been found to be definitively and entirely responsible for mouse lung remodeling during development.

The study by Yeganeh and colleagues has uncovered epithelial BECN1–mediated intrinsic autophagy as an important driver of cell death, cell differentiation, and remodeling of the lung epithelium during development; however, the role of intrinsic autophagy in the mesenchymal thinning-out process is still unclear (16). For example, Yeganeh et al. did not address how inhibiting autophagy in the epithelium might prevent mesenchymal thinning and limit capillary vascular formation. Moreover, the mechanisms that link inhibition of epithelium-specific autophagy to lineage differentiation are not at all clear. In addition, both FGF10 signaling and miRNA142-Ep300 have been implicated in these very same processes (17). If stimulating epithelial autophagy might indeed be helpful to prevent BPD, a practical challenge would be to develop a gain-of-function stimulation strategy to elicit autophagy in the right places and at the right times. Yeganeh et al., however, do point out that physiological waves of autophagy in the developing mouse lung appear to coincide with waves of AMPK activation; therefore, drugs such as caffeine, metformin, or other phosphodiesterase inhibitors might be somewhat effective as AMP-mediated, but fairly nonspecific, autophagy stimulants to potentially reverse bleomycin-induced lung fibrosis and perhaps eventually to treat BPD (18, 19).

▶ Related Article: p. 2904

Conflict of interest: The authors have declared that no conflict of interest exists.

Reference information: *J Clin Invest*. 2019;129(7):2658–2659. https://doi.org/10.1172/JCI129442.

Acknowledgments

DW is supported by the National Heart, Lung, and Blood Institute (NHLBI), NIH; the LungMAP and Fogarty International Center/National Institute of Environmental Sciences (NIEHS); the Congressionally Directed Medical Research Program (CMDRP); as well as by The Pasadena Guild of Children's Hospital Endowments and the St. Andrews Society of Los Angeles. SB is supported by grants from the Deutsche Forschungsgemeinschaft (DFG) (BE4443/1-1, BE4443/4-1, BE4443/6-1, KFO309 P7, project no. 268555672-SFB1213, and projects A02 and A04); the Landes-Offensive zur Entwicklung Wissenschaftlich-Ökonomischer Exzellenz (LOEWE); the UKGM; the Universities of Giessen and Marburg Lung Center (UGMLC); the Deutsche Zentrum für Lungenforschung (DZL); and European Cooperation in Science and Technology (COST) (BM1201).

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1. Racanelli AC, Kikkers SA, Choi AMK, Cloonan SM. Autophagy and inflammation in chronic respiratory disease. *Autophagy*. 2018;14(2):221–232.
2. Park S, et al. GOLGA2 loss causes fibrosis with autophagy in the mouse lung and liver. *Biochem Biophys Res Commun*. 2018;495(1):594–600.
3. Ghavami S, et al. Autophagy and the unfolded protein response promote profibrotic effects of TGF-β. *Am J Physiol Lung Cell Mol Physiol*. 2018;314(3):L493–L504.
4. Hu X, et al. Blocking autophagy improves the anti-tumor activity of afatinib in lung adenocarcinoma with activating EGFR mutations in vitro and in vivo. *Sci Rep*. 2017;7(1):4559.
5. Tang F, et al. SBI0206965, a novel inhibitor of Ulk1, suppresses non-small cell lung cancer cell growth by modulating both autophagy and apoptosis pathways. *Oncol Rep*. 2017;37(6):3449–3458.
6. Zhang D, et al. Autophagy maintains the integrity of endothelial barrier in LPS-induced lung injury. *J Cell Physiol*. 2018;233(1):688–698.
7. Zeng M, et al. 4-PBA inhibits LPS-induced inflammation through regulating ER stress and autophagy in acute lung injury models. *Toxicol Lett*. 2017;271:26–37.
8. Guo JY, White E. Autophagy, Metabolism, and Cancer. *Cold Spring Harb Symp Quant Biol*. 2016;81:73–78.
9. Liu X, et al. Autophagy induced by DAMPs facilitates the inflammation response in lungs undergoing ischemia-reperfusion injury through promoting TRAF6 ubiquitination. *Cell Death Differ*. 2017;24(4):683–693.
10. Liu F, et al. MiR-155 Alleviates Septic Lung Injury by Inducing Autophagy Via Inhibition of Transforming Growth Factor-β-Activated Binding Protein 2. *Shock*. 2017;48(1):61–68.
11. Deng X, et al. PM. *Biochim Biophys Acta Gen Subj*. 2017;1861(2):112–125.
12. Margaritopoulos GA, Lasithiotaki I, Antoniou KM. Toll-like receptors and autophagy in interstitial lung diseases. *Eur J Pharmacol*. 2017;808:28–34.
13. Vij N, Chandramani-Shivalingappa P, Van Westphal C, Hole R, Bodas M. Cigarette smoke-induced autophagy impairment accelerates lung aging, COPD-emphysema exacerbations and pathogenesis. *Am J Physiol, Cell Physiol*. 2018;314(1):C73–C87.
14. Mizumura K, et al. Autophagy: friend or foe in lung disease? *Ann Am Thorac Soc*. 2016;13 Suppl 1:S40–S47.
15. Pabon MA, Ma KC, Choi AM. Autophagy and obesity-related lung disease. *Am J Respir Cell Mol Biol*. 2016;54(5):636–646.
16. Yeganeh B, Lee J, Ermini L, Lok I, Ackerley C, Post M. Autophagy is required for lung development and morphogenesis. *J Clin Invest*. 2019;129(7):2904–2919.
17. Chao CM, et al. Fgf10 deficiency is causative for lethality in a mouse model of bronchopulmonary dysplasia. *J Pathol*. 2017;241(1):91–103.
18. Shrestha A, et al. MicroRNA-142 is a multifaceted regulator in organogenesis, homeostasis, and disease. *Dev Dyn*. 2017;246(4):285–290.
19. Rangarajan S, et al. Metformin reverses established lung fibrosis in a bleomycin model. *Nat Med*. 2018;24(8):1121–1127.