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Title: The role of the lysophosphatidic acid (LPA) receptor 1 in developmental alveolarization

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Body: The LPA pathway mediates multiple biological processes involved both in organ development and in remodeling in response to injury in adult life. Disrupting this pathway has been linked to defects in vascular and neuronal development. We now show that deficiency of one of LPA's receptors, LPA1, leads to defective alveolarization, resulting in an emphysema-like phenotype in mice. We found that the number of alveoli, the volume of septal tissue and the total surface area of the alveolar epithelium were significantly reduced while the mean volume of alveoli increased in LPA1-deficient (LPA1KO) compared to wild type (WT) mice. The differences in alveolar surface and septal tissue volume between LPA1KO and WT increased between 3 and 12wks, but then remained stable. The total number of alveoli increased between 12wks and 6months equally, arguing against destructive emphysema. The widening differences in surface density and area between the 2 groups after early alveolarization at 3wks indicate that a later stage of alveolarization occurs in mice and significantly contributes to lung growth. Our data show an impaired alveolarisation between 3 and 12wks, thus an defect before 3months. During early alveolarization myofibroblasts accumulate in developing secondary septae, next to a complex network of capillaries. Electron microscopy revealed no differences in the alveolar capillary bed. Instead, we hypothesize that the defect in alveolarization in LPA1KO is due to diminished accumulation of myofibroblasts. In conclusion, the LPA pathway appears to make important contributions to the process of alveolarization, possibly through its contributions to fibroblast recruitment, proliferation or differentiation.