Macrophage-derived IL-6 trans-signalling as a novel target in the pathogenesis of bronchopulmonary dysplasia

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M1-like macrophage activation is linked to IL-6/STAT3 axis in clinical and experimental BPD. Inhibition of macrophage-related IL-6 trans-signalling promotes ATII survival and lung growth in experimental BPD as a new therapy for preterm infants. https://bit.ly/3AhF7GP

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Abstract

Rationale Premature infants exposed to oxygen are at risk for bronchopulmonary dysplasia (BPD), which is characterised by lung growth arrest. Inflammation is important, but the mechanisms remain elusive. Here, we investigated inflammatory pathways and therapeutic targets in severe clinical and experimental BPD.

Methods and results First, transcriptomic analysis with *in silico* cellular deconvolution identified a lung-intrinsic M1-like-driven cytokine pattern in newborn mice after hyperoxia. These findings were confirmed by gene expression of macrophage-regulating chemokines (*Ccl2*, *Ccl7*, *Cxcl5*) and markers (*Il6*, *Il17A*, *Mmp12*). Secondly, hyperoxia-activated interleukin 6 (IL-6)/signal transducer and activator of transcription 3 (STAT3) signalling was measured *in vivo* and related to loss of alveolar epithelial type II cells (ATII) as well as increased mesenchymal marker. *Il6* null mice exhibited preserved ATII survival, reduced myofibroblasts and improved elastic fibre assembly, thus enabling lung growth and protecting lung function. Pharmacological inhibition of global IL-6 signalling and IL-6 trans-signalling promoted alveolarisation and ATII survival after hyperoxia. Third, hyperoxia triggered M1-like polarisation, possibly *via* Krüppel-like factor 4; hyperoxia-conditioned medium of macrophages and IL-6-impaired ATII proliferation. Finally, clinical data demonstrated elevated macrophage-related plasma cytokines as potential

biomarkers that identify infants receiving oxygen at increased risk of developing BPD. Moreover, macrophage-derived *IL6* and active STAT3 were related to loss of epithelial cells in BPD lungs.

Conclusion We present a novel IL-6-mediated mechanism by which hyperoxia activates macrophages in immature lungs, impairs ATII homeostasis and disrupts elastic fibre formation, thereby inhibiting lung growth. The data provide evidence that IL-6 trans-signalling could offer an innovative pharmacological target to enable lung growth in severe neonatal chronic lung disease.