Sex-specific Differences in Cell-cell Communication Patterns and Receptor-ligand Interactions in the Developing Lung: Implications for Bronchopulmonary Dysplasia

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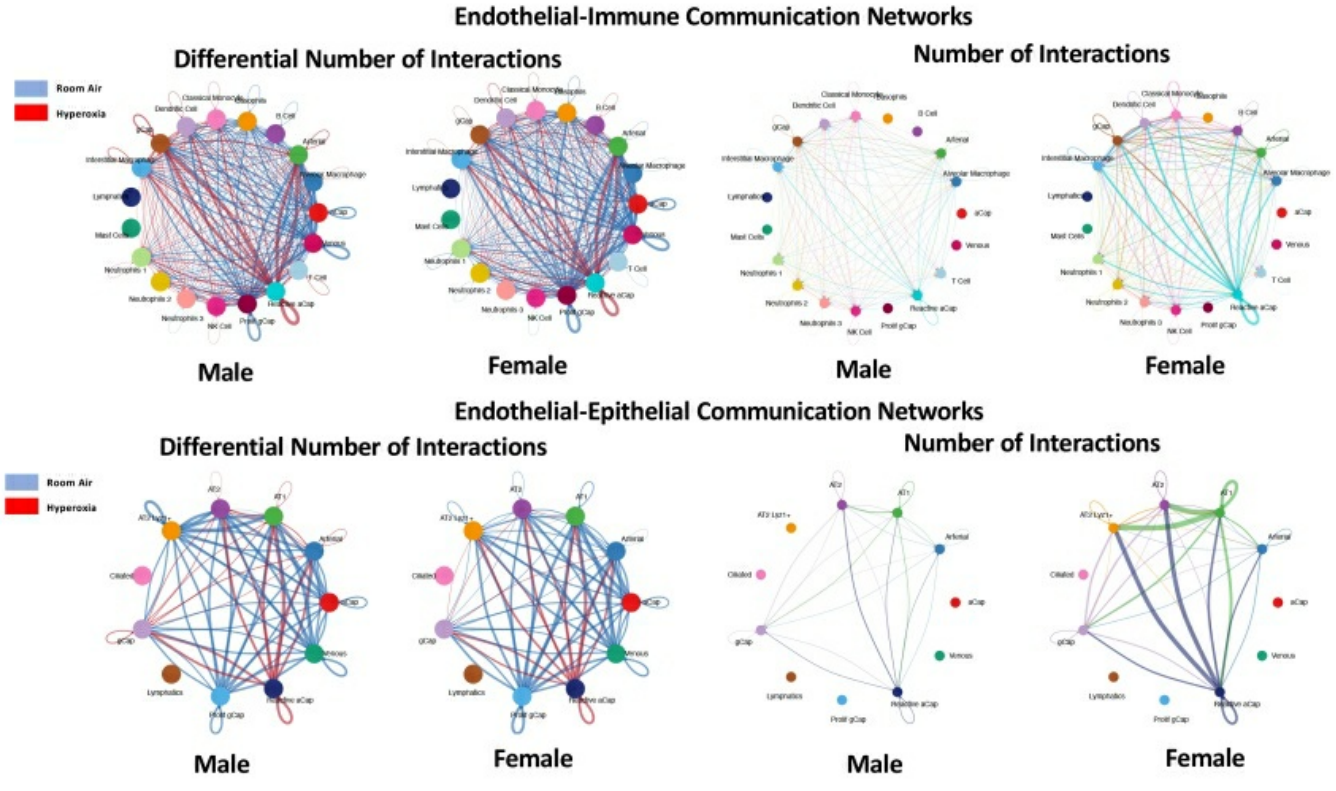
Rationale: Premature female neonates are less susceptible to the development of bronchopulmonary dysplasia (BPD), but the underlying is unknown. We have shown remarkable sex-specific differences in the neonatal murine lung when subjected to hyperoxia. We hypothesized that distinct cell-cell communication patterns modulate the injury phenotype in the male and female lung. scRNA-seq was used to elucidate the sex-specific transcriptomic differences in different lung cell sub-populations and decipher the novel cell-cell interaction and receptor-ligand interactions in the male and female neonatal lung.Methods: Neonatal WT (C57BL/6N) mice were exposed to hyperoxia (95% FiO_2, PND 1-4: saccular stage) or room air and euthanized on PND7. Viable single cells were isolated by FACS at PND5 (n=3/gp). Library preparation was completed on the Chromium 10X system. Sequencing data were mapped to mm10 and quantified using GENCODE. Data normalization, doublet removal, cell type clustering, and marker gene identification, and hyperoxia response gene signatures were performed using Seurat. RNA velocity estimation was done using velocyto, then scVelo. Cell-cell communication was analyzed using Cellchat (version 1.4.0) on room air and hyperoxia samples.Results: scRNAseq identified 22 distinct cell clusters from 35,934 cells in both hyperoxia-exposed and control lungs consistent with distinct populations of endothelial, epithelial, mesenchymal, and immune cells. Upon exposure to hyperoxia, a distinct population of distal lung endothelial cells (reactive aCaps) predicted to be arising from the gCaP (general capillary) cells were identified. Between the immune and endothelial cells, in the hyperoxia-exposed lung, reactive aCaPs (sender)- interstitial macrophage (receiver) was identified as one of the main signaling networks (greater in females than males) with ligands involving Pros 1 (Protein S), Sema 6 (Semaphorin 6) and CD200, all of which are known to modulate the inflammatory phenotype of macrophages. Interestingly, (TNF)-related apoptosis-inducing ligand (Trail) and Cell adhesion molecule 1 (Cadm1) were identified as male-specific ligands upon exposure to hyperoxia from reactive aCaPs. Reactive aCaPs were also the main senders between the endothelial-epithelial cell interaction networks. Reactive aCaP (sender) and Lyz1+ AT2 (receiver) interaction were exclusive to the female lung and the number of interactions was greater in the female lung compared to the male lung. Semaphorin 3 was a female-specific ligand, while Tgf-beta was a male-specific ligand in this interaction. Conclusions: Cell-cell communication and ligand-receptor interactions are different in the hyperoxia-exposed male and female neonatal lung. Differences in cell-cell interaction may underlie the differences in disease phenotype with implications for human disease.



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