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Identification of a novel subset of alveolar type 2 cells enriched in PD-L1 and expanded following pneumonectomy

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A novel population of AT2 progenitor cells enriched for PD-L1 has been identified. This normally quiescent subpopulation of AT2 cells becomes highly proliferative and differentiates into mature AT2 in response to alveolar injury. https://bit.ly/31G0IIW

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Abstract

Alveolar type 2 (AT2) cells are heterogeneous cells, with specialised AT2 subpopulations within this lineage exhibiting stem cell properties. However, the existence of quiescent, immature cells within the AT2 lineage that are activated during lung regeneration is unknown.

Sftpc$^{CreERT2/+}$;*tdTomato*$^{flox/flox}$ mice were used for the labelling of AT2 cells and labelled subpopulations were analysed by flow cytometry, quantitative PCR, assay for transposase-accessible chromatin using sequencing (ATAC-seq), gene arrays, pneumonectomy and culture of precision-cut lung slices. Single-cell RNA-sequencing (scRNA-seq) data from human lungs were analysed.

In mice, we detected two distinct AT2 subpopulations, with low tdTomato level (Tom^{Low}) and high tdTomato level (Tom^{High}). Tom^{Low} cells express lower levels of the AT2 differentiation markers *Fgfr2b* and *Etv5*, while Tom^{High}, as *bona fide* mature AT2 cells, show higher levels of *Sftpc*, *Sftpb*, *Sftpa1*, *Fgfr2b* and *Etv5* expression. ATAC-seq analysis indicates that Tom^{Low} and Tom^{High} cells constitute two distinct cell populations, with specific silencing of *Sftpc*, *Rosa26* and cell cycle gene loci in the Tom^{Low} population. Upon pneumonectomy, the number of Tom^{Low} but not Tom^{High} cells increases and Tom^{Low} cells show upregulated expression of *Fgfr2b*, *Etv5*, *Sftpc*, *Ccnd1* and *Ccnd2* compared to Sham. Tom^{Low} cells overexpress programmed cell death 1 ligand 1 (PD-L1), an immune inhibitory membrane receptor ligand, which is used by flow cytometry to differentially isolate these two subpopulations. In the human lung, data mining of a recent scRNA-seq AT2 data set demonstrates the existence of a *PD-L1*^{Pos} population. Therefore, we have identified a novel population of AT2 quiescent, immature progenitor cells in mouse that expand upon pneumonectomy and we have provided evidence for the existence of such cells in human.