Development of Human Lung Macrophages from Fetal and Adult Progenitors in Vivo

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Introduction
Alveolar macrophages are critical for healthy lung function, yet the origin and ontogeny of human lung macrophages is poorly understood due to the lack of suitable experimental systems. Specifically, the progenitor of human lung macrophages is unknown.
Methods
To create an in vivo model for human macrophages, we engineered human gene knock-in mice, named MISTRG, expressing critical human cytokines, such as GM-CSF and M-CSF, which allows the development of human alveolar macrophages (Nature Biotechnology 2014).
Results
Lung transplantation data indicate that human lung macrophages are independent of blood monocytes and therefore of embryonic origin. Due to the critical role of GM-CSF, we predicted that expression of GM-CSF receptor (CD116) marks alveolar macrophage progenitors in human fetal tissue. Consistent with our prediction, we identified CD116-expressing candidate progenitors in human fetal liver. To confirm the progenitor-product relationship in vivo, we transplanted fetal liver populations into the airways of newborn MISTRG recipients. These experiments showed that CD34-Lineage-CD11b+HLA-DR+CD116+ cells were able to give rise to human alveolar macrophages. Therefore, our studies demonstrate that human alveolar macrophages arise from GM-CSF receptor-expressing fetal liver progenitors.
Using our model, we have also identified the adult (blood monocyte-dependent) progenitor of human lung macrophages because blood monocyte-derived macrophages are relevant in the context of lung pathology. We found that CD14+CD16- monocytes highly express the GM-CSF receptor (CD116) and are the first monocyte subset to appear in MISTRG mice transplanted with hematopoietic stem cells before alveolar macrophages colonize the lung. Furthermore, our transplantation studies and monocyte fate-mapping support a model where CD14+CD16- monocytes convert into CD16+ monocytes that then differentiate into lung macrophages. We have also performed single-cell RNA-sequencing to define the developmental trajectory of human lung macrophages from blood monocytes.
Conclusion
Our study provides important information on human lung macrophage development that cannot be obtained with other approaches. We expect that it will lead to critical new insights that are relevant to inflammatory lung diseases in humans, which are very common, but have no cure.

Keywords : Lung, macrophage, ontogeny, progenitor, humanized mice
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