Molecular insight into cellular crosstalk during development and disease

Tissue development and function arises from interactions between diverse cell types and lineages, as crosstalk between neighboring cells underlines many biological processes, such as cell activation, differentiation and signaling. Dissection of the secreted and the direct cellular crosstalk during developmental stages will shed light on aberrant signaling pathways during the onset of a tissue-specific pathology. Using single-cell RNA sequencing (RNA-seq), we first characterized the cellular composition of the lung during development, and identified vast dynamics in cell composition and their molecular characteristics. A global analysis of ligand-receptor interaction pairs within and between cell lineages, highlighted basophils as a highly interactive cells with lung-unique gene signature, that play a role in alveolar macrophage development and function. Next, in order to focus on direct cell-cell interactions, we developed a technology of physically interacting cell sequencing (PIC-seq), which combines fluorescently activated cell sorting of physically interacting cells along with massively parallel single-cell RNA-seq and computational modeling to systematically map in situ cellular interactions and characterize their molecular crosstalk. Investigation of T – myeloid cell interactions by PIC-seq following exposure to pathogen, and in tumor microenvironment of early lung adenocarcinoma lesions, revealed an interaction-specific transcription, including upregulation of a costimulatory program in rare interactions. Together, the study demonstrates how investigation of cellular crosstalk during tissue development can broaden our understanding regarding signaling networks in health and disease. Moreover, PIC-seq technology enables to reveal rare molecular crosstalk between communicating cells essential for the priming of specific cell activation states; therefore it has the capacity to highlight novel molecular targets applicable in infectious disease, autoimmunity, tumor-immunology and immunotherapy.