Poster 31 Alveolar organoids with innate and adaptive immune cells

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Organoids have revolutionized the study of human adult stem cells, offering new insights into complex biological systems. Alveolar epithelial type 2 cells (AT2) have been difficult to grow in vitro as they spontaneously differentiate into alveolar epithelial type 1 cells. However, when cultured as 3D organoids they retain typical AT2 markers. Since organoid models are epithelium-only structures, they lack immune cells, specifically the tissue-resident immune cells which are crucial for studying immune-related diseases and drug-induced adverse events. To address this gap, we have developed a fully autologous immunocompetent human alveolar organoid model derived from fresh tissue resections. From the same resection we isolated AT2 cells for alveolar organoids, tissue-resident memory T cells and alveolar myeloid cells. The various cell types were shown to retain their functionality upon cryopreservation. The different compartments were then combined in a 3D co-culture presenting an innovative in vitro model that enables the investigation of tissue-resident immune responses specifically focusing on the role of the myeloid compartment upon T cell stimulation. This novel in vitro approach allows exploring relevant cellular interactions by single-cell RNA-sequencing and imaging revealing that the alveolar myeloid cells affect the treatment response by directly communicating with other cell types present in the culture condition. Additionally, we leveraged this immunocompetent model to study clinically relevant adverse events induced by targeted therapies and immune checkpoint inhibitors. Our findings demonstrate the potential of this model to provide valuable insights into tissue-specific immune responses, paving the way for improved therapeutic strategies and personalized medicine.