SEQUENCING

Species-specific cortex features

Nature **573**, 61–68 (2019)

The cerebral cortex is the centre of higher brain functions and regulates complex tasks such as memory, sensation and perception. The human cortex differs in size, composition, specialization and transcriptional regulation from the mouse cortex. Lein and colleagues provide extensive single-cell transcriptomics data to classify cell types and their species-specific characteristics.

The authors performed single-nucleus RNA-sequencing on human post-mortem middle temporal gyrus samples. They characterized 75 unique cell types identified and compared them to their mouse counterparts. Although the cellular architecture and transcriptomic organization of cell classes was largely conserved between species, regional and functional variation was found at deeper levels.

Among the differences observed in human compared with mouse tissue were the proportions of inhibitory neuron classes, laminar distributions, higher morphological diversity in astrocytes and also divergent gene expression and cell marker profiles. Divergent genes were often associated with signalling and connectivity. Serotonin and other neurotransmitter receptors were among the most divergent gene families, which might indicate considerable functional differences.

The study exemplifies the species-specific complexity of the cortex and highlights why preclinical analysis in the mouse might not always be readily translatable into therapies. *CW*

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SEQUENCING

Single-cell spatial transcriptomics

Science **373**, 111–117 (2021)

Single-cell RNA sequencing (scRNA-seq) reveals gene expression profiles of individual cells, but does not take into account the positional information of nuclei or RNA. Spatial transcriptomics approaches use tissue sections, DNA-barcoded beads or in situ hybridization to retain this positional information, but struggle to resolve individual cells, or require extensive processing.

Trapnell and colleagues build on their previous method, sci-Plex, which uses single-stranded DNA oligonucleotides to label nuclei, followed by scRNA-seq. Their latest technique, sci-Space, captures positional information by introducing oligo arrays onto tissue sections, imaging and labelling them with section-identifying barcodes for scRNA-seq.

Applying this approach to embryonic day 14 (E14) mouse embryos, sci-Space detected spatially and cell-type resolved expression patterns across the embryo and data readily integrated and overlapped with published mouse scRNA-seq profiles. Although spatial resolution was limited to approximately 200 µm, unlike other spatial transcriptome capture methods, sci-Space recovered the single-cell transcriptome, distinguishing gene expression patterns in individual cells from those in groups of cells. A statistical approach confirmed that spatial differentiation gradients seen with sci-Space recapitulate known differentiation patterns of migrating neurons.

sci-Space provides spatial transcriptomics at single-cell resolution, a powerful expansion of the single-cell atlas toolbox. *CW*

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SEQUENCING

COVID-19 lung atlas

Nature **595**, 114–119 (2021)

Severe COVID-19 cases are often accompanied by complex host responses that involve diverse cell types. Using a powerful single-nucleus RNA sequencing approach, Izar and colleagues focus on cellular changes in the lungs of 19 patients who died of COVID-19.

The authors identified myeloid cells as the dominant source of dysregulated inflammation in COVID-19 and found evidence of impaired T cell responses. Compromised lung regeneration could be traced back to a failure of alveolar type 2 (AT2) cells to transition into AT1 cells, as observed during normal repair. Instead, AT2 cells persisted in a transient, intermediate progenitor state previously described in fibrotic lung injury.

Further analysis pinpointed the cellular sources of inflammatory cytokines, such as IL-1β, IL-6 and interferons that contributed to the hyperinflammatory environment and probably also the transient state. The authors concluded that myeloid-derived IL-1β might be one of the distinguishing factors in COVID-19 pathology, separating it from other viral or bacterial infections. Increased numbers of pulmonary-fibrosis-promoting fibroblasts were also described.

The atlas describes SARS-CoV-2 lung pathology at a single-cell level and provides an important resource for the evaluation of disease complications and therapeutic options. *CW*

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SEQUENCING

An endoderm reference atlas

Cell https://doi.org/10.1016/j.cell.2021.04.028 (2021)

Endoderm-derived epithelial stem cells have varying roles in human organ development and undergo complex differentiation patterns. Camp and colleagues combine a single-cell transcriptomics atlas and organoid models to reconstruct human intestinal development and evaluate the extent to which it can be modelled by organoids.

The authors integrated generated and published single-cell transcriptomics data from human lung, oesophagus, liver, stomach, small intestine and colon samples, 7–21 weeks after conception. They analysed 155,232 cells for a comprehensive map of cell populations and their molecular profiles.

Intestinal organoids were generated from embryonic stem cells and transplanted into mouse kidney capsules, followed by single-cell sequencing 4 and 8 weeks later. The similarity of these organoids to the atlas data was quantified by calculating the distance of each organoid cell to its atlas counterpart, 70% of which mapped to the developing human intestine.

Using single-cell data from the developing and adult duodenum as a reference, organoid stem cells were confirmed as closely related to the developing intestine. Time courses, maturation and trajectory analyses allowed comprehensive reconstruction of intestinal development and interactions between mesenchymal and epithelial stem cells, and specific effects of regulators such as NRG1, EGF and CDX2. *CW*

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