News & views

Transcriptomics

Reference maps for the human body

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The HuBMAP consortium has generated spatially resolved cell atlases for the human intestine, kidney and placenta, which enable analysis of tissue organization in unprecedented detail. **See p.572, p.585 & p.595**

The trillions of cells of the human body must be arranged in precise patterns for tissues and organs to function properly. The HuBMAP initiative[1] aims to generate the technology and resources needed for researchers to map how cell types are arranged throughout the body, as well as producing its own maps of several organs. In doing so, HuBMAP should provide researchers with tools to better study the complexities of human tissue organization in health and disease. Three papers in this issue mark a key step for the initiative, describing reference cell atlases for the human placenta[2], intestine[3] and kidney[4].

Single-cell transcriptomics methods are used to identify all the RNA transcripts in single cells or nuclei, and thereby reveal the gene-expression profile of each cell. In doing so, these methods give researchers a 'parts list' of cell types in a tissue of interest. Emerging spatial methods put these parts together in context, thereby generating cell-level maps of tissues. Spatial methods for measuring molecules in tissues are broadly categorized into sequencing and imaging-based approaches.

One of the most-used sequencing-based spatial methods is spatial transcriptomics. In this approach, slices of the tissue of interest are placed on a specially prepared microscope slide. The RNA from each cell binds to a short string of nucleotides[5] that contains a molecular barcode, which is unique to that position on the slide (each position is known as a voxel and approximately corresponds to between 5 and 40 cells). A newer version of this technology that enables subcellular resolution uses molecular-barcoded beads with known positions[6]. In both cases, RNA sequencing is performed outside the tissue, and spatial information is reconstructed using the barcodes attached to each RNA sequence. Integration with matched single-cell transcriptomics data (which provide non-spatial information about which cell types express which genes) enables researchers to measure the approximate proportions of each type of cell in each voxel.

Imaging-based methods can quantify the relative levels of proteins (or transcripts) at the single-cell level. To image proteins in parallel, scientists use antibodies for a panel of proteins, tagged with either heavy-metal isotopes (a technique called MIBI)[7] or DNA barcodes (CODEX)[8]. The metal isotopes can be imaged using a type of mass spectrometer that scans across the tissue. The DNA barcodes interact with complementary molecules called probes that carry fluorescent tags, and can be detected through fluorescence microscopy (Fig. 1). These methods enable the accurate quantification of proteins expressed by each cell, as well as the definition of cellular neighbourhoods (groups of cells surrounding a specific cell) that underpin a tissue's architecture. However, the panels of proteins under investigation need to be defined in advance, and only a few tens of proteins are usually measured in parallel.

On page 595, Greenbaum *et al.*[2] used MIBI

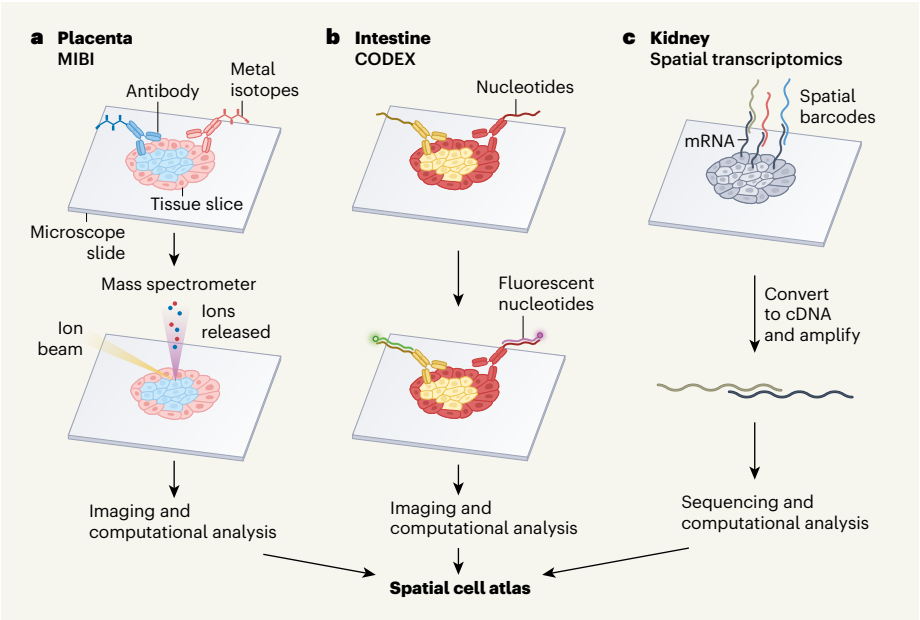

Figure 1 | Single-cell atlases generated in three ways. The HuBMAP initiative has mapped the organization of all cell types in the human placenta[2], intestine[3] and kidney[4]. **a**, Greenbaum *et al.*[2] mapped the placenta (as well as maternal tissue around it) using a technique called MIBI. Slices of placenta are placed on a microscope slide and treated with a panel of antibodies, each of which is attached to a different type of metal isotope. An ion beam scans the slide, releasing ions from the isotopes that are detected by a mass spectrometer. Computational analysis of the ions reveals the relative levels of protein produced in each cell — information that is then used to identify cell types at each point in the tissue, producing a cell atlas. **b**, Hickey *et al.*[3] mapped the intestine using a related technique called CODEX, in which each antibody is attached to a different nucleotide sequence. Nucleotides carrying a fluorescent molecule bind to their complementary antibody-bound sequence and fluoresce. Fluorescence microscopy is used to produce the cell atlas. **c**, Lake *et al.*[4] used spatial transcriptomics to map the kidney. The microscope slide is prepared such that tiny regions contain nucleotide-based spatial barcodes. Each messenger RNA in each cell binds to a barcode. The RNA is converted to complementary DNA (cDNA), amplified and sequenced, and the barcodes are then used to determine mRNA-expression profiles in each region of the slide, generating the cell atlas.

to obtain a cell-level map of the human placenta — specifically, the interface between the fetal placenta and the maternal uterine wall. They used slices of placenta from 66 terminated pregnancies, focusing on those in which placental cells were invading the wall of the uterus — a crucial event that remodels maternal arteries in such a way as to deliver blood to the areas in which maternal and fetal cells interact, without damaging the delicate placenta. Using MIBI enabled the authors to profile multiple samples at different stages of development and to define interactions between placental and immune cells at single-cell resolution.

Through analysis of the maps, the authors identified how maternal immune cells promote a tolerant environment (its niche) in the region in and around the artery, which allows peaceful coexistence between genetically distinct maternal uterine and fetal placental cells. Combined with recent spatial transcriptomics of the placenta[9], Greenbaum and colleagues' discoveries deepen our understanding of the maternal vascular transformation that sustains embryonic development.

Hickey *et al.*[3] (page 572) focused on the intestine — a complex organ that exhibits highly diverse structures and functions along its length. The authors used CODEX and single-nucleus transcriptomics to map eight sites along the intestine, using samples from nine people. The authors discovered drastic shifts in cellular composition and organization between the sites. They found previously unknown subtypes of epithelial cell (the cells that line the intestine), which were arranged in distinct neighbourhoods. They also define immune-cell-rich neighbourhoods where immune cells can be readily activated if required. Overall, the findings reveal that specialized anatomical regions in the intestine are underpinned by highly structured spatial niches, each with unique functions. Such insights could only be gained using spatial methods.

Lake *et al.*[4] (page 585) examined 45 healthy and 48 diseased kidneys. The authors defined the locations of cells that adopt previously unidentified states during acute kidney injury or chronic kidney disease, including maladaptive tissue-repair states that might hinder the formation of kidney tubules after injury. Spatial mapping revealed cell–cell communication between maladaptive cells and other fibrotic (tissue-scarring) and inflammatory cells. The authors also identified transcriptomic signatures associated with a state of cell dormancy, called senescence, that might underlie the progression to kidney failure.

Both Hickey *et al.* and Lake *et al.* complemented their spatial atlases with single-cell 'open chromatin' assays, which provide information about the active transcription factors in a cell. Combining their various approaches enabled the authors to define the transcription factors that mediate cellular identities in different tissue niches. These studies are a powerful example of how incorporating these types of assay with spatial analyses gives a coherent picture of cell identity in context.

Altogether, the three papers demonstrate how spatial methods are empowering scientists to analyse tissues and organs at unprecedented resolution, providing standardized ways to generate cell atlases. The three HuBMAP atlases also have the potential to advance our understanding of disease, by defining the spatial location of cell states linked to disease and by helping to contextualize genome-wide association studies — which can link particular genetic variants to a disease, but provide no spatial context to indicate in what cell type that variant might exert its effect. We anticipate that this work, along with several HuBMAP papers published in other journals (see go.nature.com/3rxansc), will inspire the generation of spatial atlases in other tissues.

Looking to the future, these studies highlight the continued need to advance spatial technologies. The number of assays that can be performed on single-tissue slides must be increased to enhance the ability to study cells at subcellular resolution and begin to move from studies performed in 2D on slides towards true 3D reconstruction. The number of samples analysed must also increase, so that researchers can correlate spatial organization with other information such as body mass index or disease stage. Such correlations could provide clues to how disease progresses in specific locations in the body.

Increasing the breadth and depth of spatial technologies will ultimately establish robust associations between cellular organization and function in health and disease. The current studies provide an outstanding contribution to this aim.

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The authors declare no competing interests.

In retrospect

Proof of the electroweak force 50 years on

Pippa Wells

The discovery of 'weak neutral currents' at Europe's particle-physics research centre CERN 50 years ago was a decisive step towards establishing the standard model of particle physics — a journey that continues to this day.

July 2023 marks the 50th anniversary of one of the greatest discoveries made at CERN, the international particle-physics research centre near Geneva, Switzerland: namely, weak neutral currents. The discovery, made by the Gargamelle experiment, provided key evidence that one of four known fundamental forces in nature, the weak interaction, is inextricably entwined with another, the more familiar force of electromagnetism. That finding opened a path of exploration that led, by way of numerous breakthroughs, to the discovery of the Higgs boson in 2012 — and it is still revealing new and exciting perspectives today.

The influence of the weak interaction is seen most obviously in radioactive β-particle decays. When CERN was founded in 1954, particle physicists' understanding of the interaction was in its infancy. Back then, the best way to study matter and its workings at the smallest scales was to fire high-energy beams of particles into a target and measure what emerged.

In 1959, CERN's Proton Synchrotron accelerator started up. This could produce beams of various particle types, and in the early 1960s, experiments began there with the extremely light particles known as neutrinos — albeit with fierce competition from the higher-energy Alternating Gradient Synchrotron, situated