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Human Cell Atlas hopes to unravel mysteries hidden in our genes

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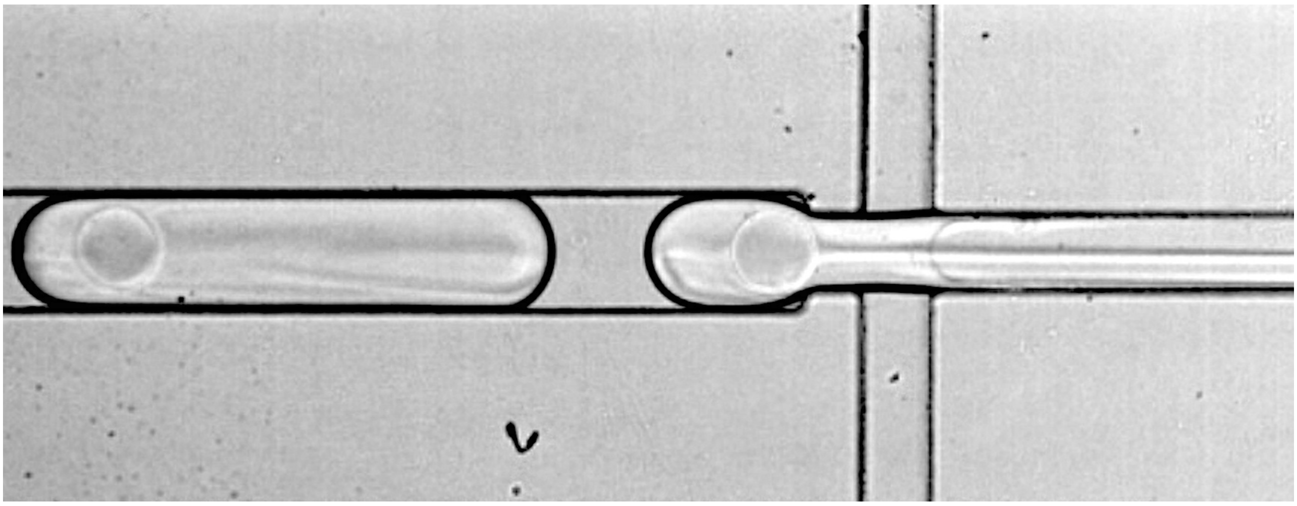

A process called droplet microfluidics isolates thousands of cells in microscopic water droplets allowing up-close analysis of genetic material. Image credit - Dr Linas Mazutis

A major international project is attempting to create the first comprehensive three-dimensional map of all human cells which could end up revealing secrets about our health and how our bodies function.

It is nearly 350 years since scientists first discovered that our bodies are made up of tiny building blocks known as cells. Today we still know very little about their nature, but if we did, we could better understand how our bodies work, how diseases afflict us and how we age.

A global project called Human Cell Atlas is now attempting to create the first comprehensive three-dimensional map of the human body in order to unravel some of these mysteries.

‘It will hopefully have the same impact as when the human genome was sequenced,’ said Dr Linas Mazutis, a biochemist at Vilnius University in Lithuania. ‘A human cell atlas could set the stage to develop new technologies and provide new answers about the human body.’

The project could also lead to better diagnosis and treatment of diseases, but taking a census of all human cells is no simple task – there are an estimated 40 trillion in each adult body.

Dr Mazutis coordinates an EU-funded project called Cells-in-drops, which is aimed at developing some of the techniques needed to create this enormous map of human cells.

Their technology allows thousands of individual cells to be rapidly isolated into microscopic water droplets around 100 micrometres across – about the same width as a human hair.

Known as droplet microfluidics, this approach can be loaded with biochemical reagents that break open the cells, spilling their contents into the water they are encased in.

This essentially turns each droplet into a microscopic test tube where the genetic material, or its other contents, can be analysed.

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>
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‘We are particularly looking at gene expression programs of single cells,’ said Dr Mazutis.

This is important as not all genes, or DNA, in every cell in the human body are switched on – in some tissues certain genes are deactivated while others are amplified.

DNA can also be read in different ways depending on the cell it is in, meaning different proteins can be produced from the same genetic code.

To help unravel this complexity, Dr Mazutis co-developed a technique with colleagues at Harvard University that analyses another type of genetic material called ribonucleic acid (RNA).

Barcoding

RNA plays an important role in cells by helping to translate the DNA code into proteins the cell needs to grow or replicate. Analysing this can then reveal details about a cell’s activity and functions.

The technique used by Dr Mazutis converts the RNA from a cell in one of the microdroplets back into DNA, but adds a unique barcode into the sequence of genes. The genetic material from all of the droplets are then pooled together and analysed in bulk.

As the genetic material from each droplet has been labelled with a barcode, it means the RNA sequences from each cell can be individually identified.

Compared to previous techniques, which required separating cells into 96 individual wells on a plastic plate, it is orders of magnitude faster and cheaper, something that will be essential for building the Human Cell Atlas.

Doing this for 40 trillion cells, however, will generate staggering volumes of data, requiring expertise from around the world in many different disciplines, but scientists are already seeing what may come out of it.

Professor Ehud Shapiro, a computer scientist and biologist at the Weizmann Institute of Science in Rehovot, Israel, said: ‘The Human Cell Atlas 1.0 is trying to map all cell types in the human body.

‘Once that is achieved, the thought is to look at questions of cell lineage to produce a sort of 4D atlas of human cell development over time.’

Cellular history

The first multi-cellular organism to have its cellular history mapped was a tiny 1 millimetre-long nematode worm called *Caenorhabditis elegans*. Composed of just 1 000 cells when fully grown, the worm was filmed as it matured from a cell into an adult, allowing scientists to follow its development.

This feat has not been repeated with any larger organism due to the difficulties in tracking cells in this way. But Prof. Shapiro and his team are developing techniques that allow them to reconstruct the lineage of cells in the human body, using tiny errors that occur in parts of the genome known as microsatellites.

These are composed of long repeats of the same code, which suffer errors as the DNA is copied when cells divide and replicate.

Prof. Shapiro and his colleagues calculated that they could reconstruct the family tree of a cell if they could track one million of these errors in its DNA. But so far it has only been possible to examine just a few hundred microsatellite errors in each cell.

However, Prof. Shapiro has being developing new techniques to look at thousands and even tens of thousands at a time.

In a project funded by the EU's European Research Council, called LineageDiscovery, he is now working on an advanced technology called padlock, or molecular inversion, which uses open loop-shaped genetic probes to target potential sites of errors.

‘So far we can use 12 000 padlock probes at once and we are now working on using 50 000 probes,’ explained Prof. Shapiro. ‘It makes a million probes seem not so far away.’

If successful, unlocking the human cell lineage tree in this way could answer some of the fundamental questions bothering biologists today. For example, it could help uncover why some cancers spread to new areas in the body.

‘Do they originate from a single cancer cell that escapes into the blood stream, or is there continual leakage from the primary tumour and there are thousands or millions of cells that independently create metastases? We are still far away from a definite answer,’ said Prof. Shapiro.

Similarly there are many questions about human development that could be answered too, like which tissues in the body can regenerate during adulthood. But before these can be answered, according to Dr Mazutis, scientists must overcome a few hurdles.

‘We don’t know how different the human cell atlas of one person will be from that of another. This all means building a human cell atlas is going to be a huge challenge,’ he said.

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More info

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