Single-cell RNA sequencing enabling individual disease treatment

The revolutionary single-cell RNA sequencing (scRNA-seq) measures the activity of all genes separately in each cell, giving a more accurate picture of how cells differ from each other. This technology will produce a vast amount of information on diseases, such as cancer. There are millions of cancer cells in a tumour. Data analysis requires increasingly more computing capacity and efficient algorithms as the number of cells and samples analysed increases.

RNA transports the manufacturing instructions in the cell from the DNA to the proteins. RNA contributes to gene expression, that is, the production of a protein that corresponds to the gene. Single-cell technology enables the measurement of RNA levels in all genes of each individual cell.

A single tissue sample of a patient can with modern technology be used to profile thousands, sometimes even tens of thousands of cells. We can reliably profile which type of cells it contains.

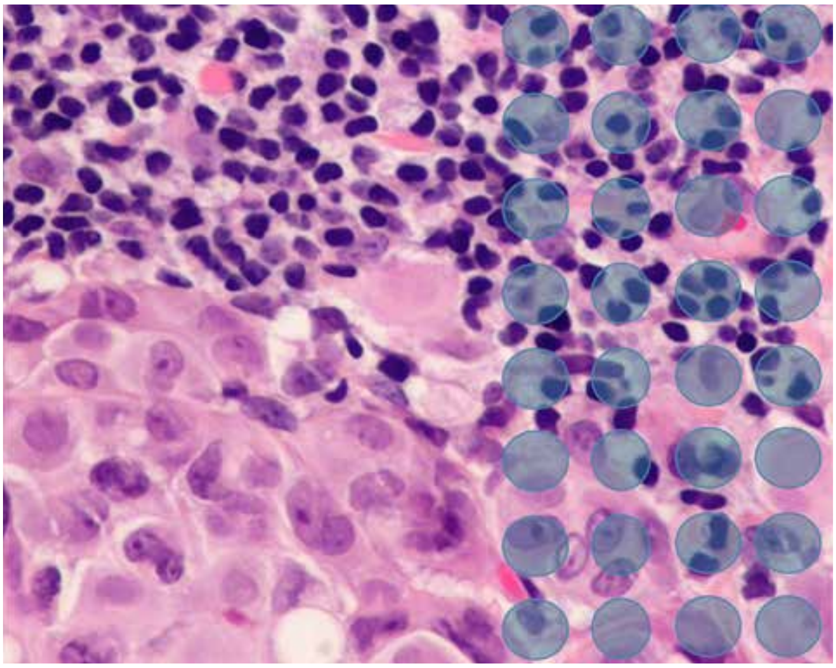
"Even if the cells may look identical under the microscope, their function may turn out to be quite different once we are able to view gene expression with single-cell accuracy," says researcher **Päivi Saavalainen**.

Saavalainen works at the Folkhälsan Research Center and she is also the CEO of a company called SCellex that specialises in single-cell technology. Saavalainen, who together with the Finland ELIXIR Node of CSC has organised single-cell analytics courses for researchers, considers single-cell technology one of the most revolutionary methods in biosciences over the last few years.

"In cancer research, for example, it is important to obtain information about a single cell. The fact is that cancer cells change all the time, meaning that each cell begins to be different. There are also gene mutations, as a result of which certain genes are activated and others deactivated."

Saavalainen considers single-cell resolution important also in the study of healthy tissues as we can find out what kind of cell types are found.

"Single-cell resolution has created a huge amount of new information for basic research alone. It was thought for a long time that humans have about 200 types of cell, but single-cell analyses have already identified more than 500."



The locations of the cancer cell RNA-profiles in the tissue slice are determined with a machine learning model.

New information about cancer cells

Thanks to the new technology developed by SCellex, it is possible to determine from the tissue structure what type of cancer cells the tumour contains and whether a mutation, for example, has only affected a certain part of the tumour.

"Now we are able to find out accurately whether, for example, a tumour contains some cancer cells that are drug-resistant and what they are actually like," says Saavalainen.

According to Saavalainen, immunotherapies for cancer have also developed dramatically. This works by helping the body's own immune cells, T-cells, to identify and kill cancer cells. A T-cell is one of the two types of lymphocyte, along with the B-cell. They identify foreign structures and help kill cells infected by a virus and also cancer cells in which mutations have changed their own genome and consequently the proteins.

"Cancer cells are trying to escape from T-cells. They keep their changed structures hidden and secrete cytokines that silence T-cells. The goal with drug treatment is to allow T-cells to penetrate tissue, identify cancer cells aggressively and kill them. Now we are able to find out, for example, what a cancer cell next to a T-cell is doing. Is it creating some gene product that silences the T-cell, and how is the T-cell reacting to that?"

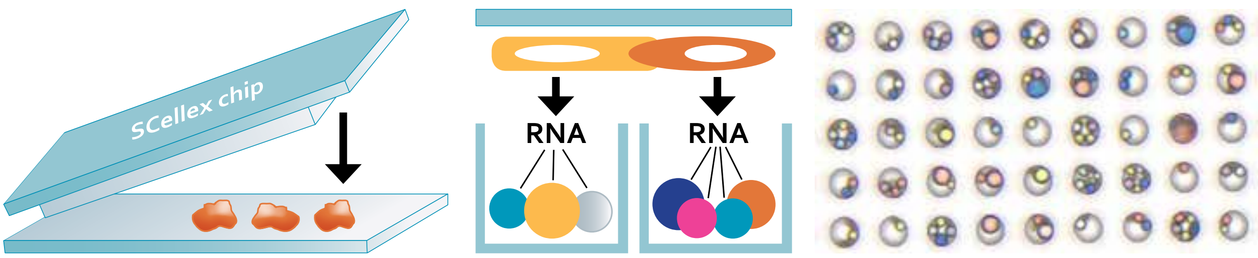
According to Saavalainen, the best-case scenario is that we understand the cancer cell types of each patient and find an effective drug to which the patient responds well. This mean we may be able to find means for individual treatments.

Spatial sequencing giving cell locations

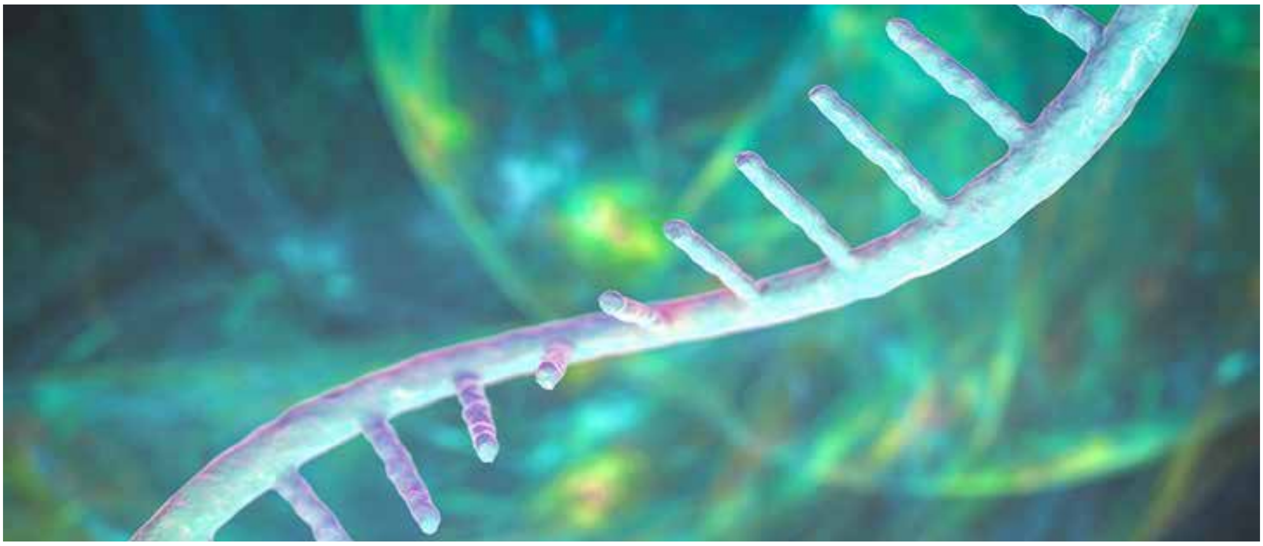
Single-cell analytics is generally performed by gently separating the cells from the tissue and transferred individually into a solution, followed by sequencing of the RNA contained in them. However, the problem with this approach is that the original location of the cells and their order in the tissue will be lost, meaning we do not know which cells were originally next to each other. Thanks to modern spatial techniques, the cells no longer have to be separated in individual solutions; you simply slice layers only one cell in thickness from the tissue, with RNA obtained directly from such layers. As the RNA is sequenced, we know which cell and which part of the tissue the RNA originated from.

"This means we can sequence tissue and still know their location and maintain their original order. Spatial sequencing is one of the hottest things at the moment," says Saavalainen.

SCellex is developing a patented technology to determine the location of cells with machine learning models and microscopic colour beads. The beads are placed into a 160,000 picowell chip array platform and their random combinations create visual coordinates for the wells that can be calcu-



The AI model used for analysing microscopic images was developed with the software of Finnish company Aiforia Technologies.



lated from the microscopic images by means of an AI model. The synthetic DNA codes attached to the microbeads are combined with the RNA molecules released from the tissue slices on the chip array platform, thereby linked to the well coordinates.

"We are using an AI model that can compute automatically which beads are in each well. In other words, AI creates a map. After this the actual tissue section can be connected to the chip, after which the synthetic DNA strands glued to the colour beads are attached to the RNA from the tissue. The RNA molecules are attached to these strands and identification is made."

"When RNA is sequenced in large batches, the data can be analysed to determine which colour bead combination the RNA matches, and then compare it with the original microscopic image and the AI computation. This way we can arrange the RNA data in their proper places."

The datasets are huge and the services of Finland ELIXIR Node of CSC can help to perform the computation. Saavalainen says that the AI models are vital.

"If a sample contains tens of thousands of cells and all of them are subject to tens of thousands of gene measurement results, then not only the data on the microbeads but also the actual biological RNA data is immensely complex. You need AI to analyse it. AI can find such new information that simply would not be possible with traditional analysis tools. I think the computing power of CSC is sufficient even to solve our challenging AI models."

Saavalainen says that the single-cell method is not yet mature enough to be used for diagnostics or prescription of drug treatments. However, at the moment it is a good tool for research purposes.

16.5.2023 | ***Ari Turunen***

MORE INFORMATION:

Folkhälsan
https://www.folkhalsan.fi/en/

Scellex
www.scellex.com

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