【Grant-in-Aid for Scientific Research (S)】

Development of ultra-sensitive high-throughput single cell elemental analysis system and creation of single cell metallomics

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Purpose and Background of the Research

●Progress in Single Cell Analysis

In recent years, research on "single cell analysis," which analyzes genes and proteins in human organs and other cells on a cell-by-cell basis rather than as an average of many cells, has been conducted worldwide. On the other hand, trace metals contained in cells have been found to play a major role in the development of various diseases such as cancer and Alzheimer's disease, as well as in the maintenance of health. At present, however, the amount of metal elements contained in many cells, ranging from tens of thousands to millions of cells, is measured and used in medical and life science research. This is because there is no instrument capable of measuring multiple trace elements in a single cell with ultra-high sensitivity.

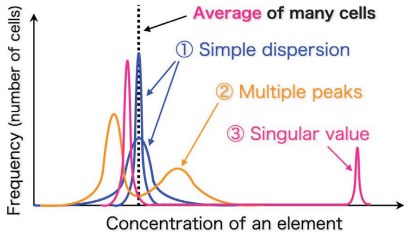

Fig. 1 Frequency distribution of metal element concentrations in a single cell

● What we hope to achieve in this research

The current general metal element analyzers measure the average concentration of metal elements in many cells, which is marked by the black dotted line in Fig 1. However, we have no information on the distribution of this average value, such as science). whether it is due to cell-specific variations, as in the blue line, or whether it can be divided into two parts, as in the orange line, or whether it contains a singular value, as in the red line. For example, this particular value may be due to abnormal cells, and there may be hints of various diseases in it.

The goal of this research is to develop a system that can reveal the distribution of metal elements as shown in Fig 1. Then, using the information on intracellular trace amounts of metals that can be analyzed by the device, research on single cell metallomics (bio-metallurgy-assisted functional science) will be started.

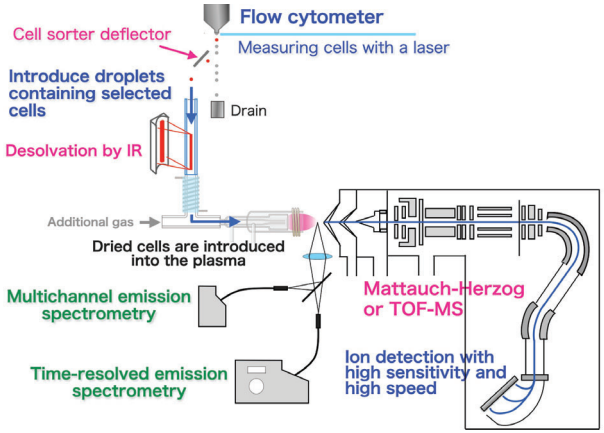

Fig. 2 Overall view of the system to be developed

Figure 2 shows the overall view of the system to be developed. This device will integrate the single-cell droplet sample introduction method for high sensitive analysis of cells, and ultrafast data acquisition method, which the principal investigator has developed in previous studies, and develop equipment incorporating various new ideas, such as infrared heating of droplets. Furthermore, by directly connecting and using a flow cytometer with a cell sorter that can extract only the desired cells from more than 10,000 cells per second, we aim to analyze up to 500 cells per second with a high degree of reliability.

Expected Research Achievements

● Ultra-Trace Element Analyzer in Single Cell: Metal Cytometer

In this study, "Ultra-Trace Element Analyzer in Single Cell (Metal Cytometer)" will be developed using several original technologies. First, cells are sorted by type using a flow cytometer capable of sorting tens of thousands of cells per second in real time. Then, only the target cells are extracted using a cell sorter and introduced into high-temperature plasma at approximately 6,000°C for analysis.

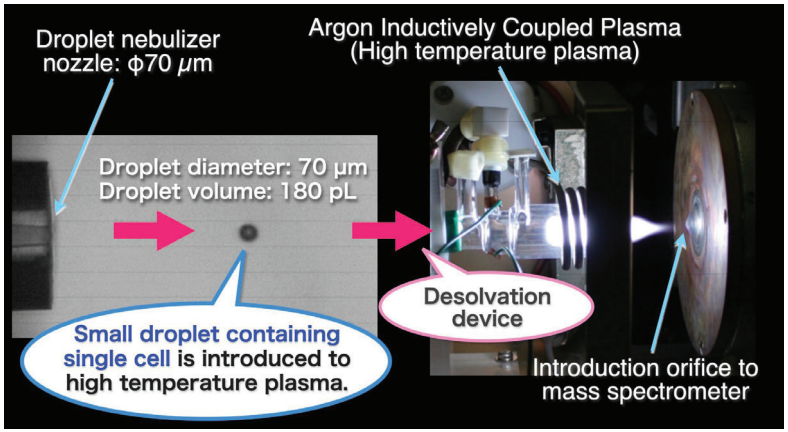

Fig. 3　Image of system to be developed

Since a single cell cannot be measured twice, it is necessary to measure all elements at one time, from high abundance elements such as calcium to very low abundance elements such as zinc and selenium. Therefore, elements with relatively high concentrations are analyzed by emission spectrometry. For elements of low concentration, the ions generated in the plasma are introduced into a mass spectrometer.

Using the developed system, ultra-trace element analysis in single cells of cancer cells and immune cells (derived from human or human iPS cells) will be performed, and the variation and uneven distribution of various metallic elements will be evaluated in detail for the first time to analyze their relationship with various cell functions. In other words, single cell metallomics research will be realized for the first time. The system to evaluate the efficacy of drugs on a cell-by-cell basis will be established using trace element bias as an indicator, and analytical equipment and technology will be established as one of the foundations of medical, pharmaceutical, agricultural, and life sciences research, with a focus on cancer treatment and regenerative medicine.

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