Development of ICT Technologies using Biological Cells

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Bio-inspired ICT technology has been awaited for innovation of ICT technology. DNA is the most fundamental material of living organisms, producing molecular machines, controlling the biological system, and transmitting genetic information. To understand how the cell is controlled by the genetic information of DNA, we have developed state-of-the-art technologies of fluorescence imaging and gene expression analysis. Here we describe current understandings on the biological system based on DNA as information materials, and future perspectives for next innovation of ICT technologies.

1 Introduction

The human body is made up of around 6 billion cells, all of which are involved in communication of information in one way or another. The cell is an advanced information processing machine: using the enormous number of molecules (around 10 billion protein molecules alone) that form and operate complex networks, it processes information about the outside world, transmits the information to the cellular nucleus, and draws out genetic information from the DNA inside its nucleus. The brain is also a superb machine that carries out complicated processes such as information processing and cell division. We are convinced that studying these systems and the driving principles behind them will lead to the creation of ICT that transcends current technology.

The question then is, what must we do to create ICT that takes advantage of the exemplary information processing capabilities of a cell? The most important thing is to gain an understanding of cellular systems. An accurate understanding of these systems will enable us to utilize the behavior of biological systems in building artificial systems. Based on this philosophy, we have been developing imaging technology to gain a better understanding of cells and technology for measuring the amount of gene expression, i.e., technology for measuring the amount of information that a cell reads from its DNA.

It is no exaggeration to state that one area of future ICT will involve the development of interfaces between communication media and cells, with communication systems of the future being able to be implanted into a living body. One of the many advantages of developing bio-ICT is the ability to direct artificial cells customized to the needs of their objectives. This will have applications in healthcare, food management, and a variety of other fields. To build an appropriate interface with cells will require comprehensive knowledge of the mechanisms behind the control of cellular systems and DNA information processing. We have been developing technology for artificially modifying cells and creating artificially enhanced cells, and we are engaged in the technological development of interfaces between cells and artificial material. In this paper we will report on development in these areas of bio-ICT.

2 Research and development to gain insights into biological systems

2.1 DNA governance

Organisms utilize DNA as a type of recording device. DNA is shaped like a spiral staircase, with the step-like parts formed by base pairs (Fig. 1: Left). These base pairs act like a recording device storing information in the way they are sequentially positioned (the nucleotide sequence). These nucleotide sequences have areas containing code on protein information with headers attached to them for cueing the reading of information. RNA molecules are read from these code areas in accordance with information contained in the headers. The DNA of human cells consists of around 6 billion base pairs (around 3 billion base pairs are inherited from each parent). This amount of information is equivalent to around 2 gigabytes of computer memory. Thus, a single fertilized egg uses a mere 2 gigabytes of information to create a system as advanced

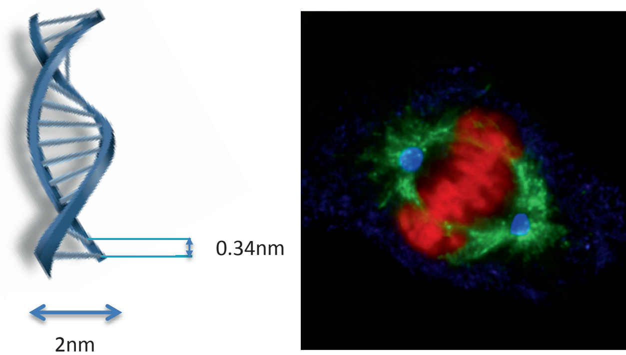

Fig. 1 DNA as an information device used by living organisms
On the left is a schematic diagram of DNA. On the right is an image of a human cell during cell division. The image represents DNA in red, microtubules in green, and centrosomes in blue.

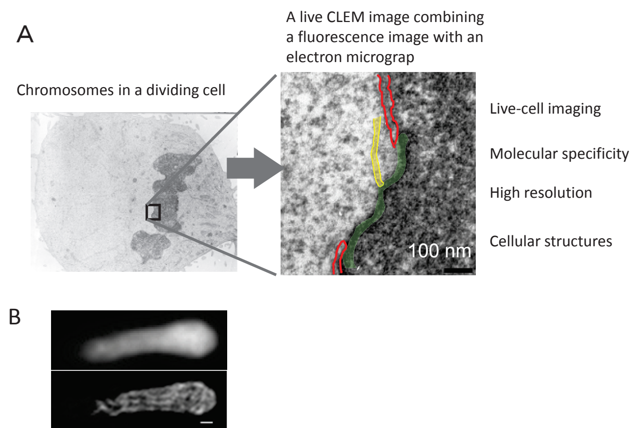

Fig. 2 An imaging method that allows live cells to be observed under high resolution
A) A dividing human cell observed by the live CLEM method. The dark mass seen in the cell shown in the left panel is the DNA. In the right panel, the DNA-bridging protein BAF is shown in green, the nuclear envelope is shown in red, and yellow shows the position of a single microtubule. The bar represents 100 nm.
B) The DNA (chromosomes) inside the nucleus of a fission yeast cell. The upper image shows what it looks like when seen through an ordinary microscope. The lower image shows chromosomes observed through 3D-SIM. The ordinary microscope shows the chromosomes as a hazy mass while 3D-SIM shows the chromosomes as a fibrous structure. The bar represents 500 nm.

as the human being. RNA is synthesized by the DNA in accordance with external environmental cues, and proteins are synthesized in turn by the RNA. This is how the information contained in the DNA is converted into protein parts. What information is expressed (switched on) and what is not (switched off), or in other words the controlling of this DNA switch is what determines the biological activities of an organism. For example, the iPS cell developed by Professor Shinya Yamanaka expresses four protein factors to reset differentiated cells, reverting them back to undifferentiated cells. These four factors completely change the gene expression pattern of the DNA and reset the cell system. The controlling of the DNA switch is the "DNA governance" system that determines the functions of the cell systems.

2.2 Imaging technology to allow visualization of the DNA inside cells

Understanding the information processing system of living organisms requires an understanding of the behavior of DNA within the cell, and directly observing the behavior of DNA within a living cell is the most straightforward method. In the early 1990s when we began our research, there was no technology for observing DNA within live cells over a period of time. Overcoming this problem led to the development of the multicolor 3D fluorescence microscopy system. The device was designed so as not to weaken cells with a powerful excitation light. We succeeded in observing structural changes over time within the cell, such as structural changes of the DNA and microtubules, as three-dimensional images (Fig. 1: Right). The response to our results was considerable and news of it was reported widely on the front page of newspapers across the country, including The Yomiuri Shimbun and The Sankei Shimbun[1].

When we used this system to examine DNA inside cells, we directly observed that the long DNA molecules of a human cell (2 meters of DNA copies itself to become 4 meters of DNA) are divided evenly between two daughter cells (2 meters each) in a short time (around 30 minutes) during mitosis. We also discovered that when fission yeast become depleted of nutrients the spatial arrangement of the DNA within the nucleus changes drastically, changing from a "centromere-clustering" structure in which three centromeres are clustered at the position of the spindle pole body (SPB) to a "telomere-clustering" structure in which six telomeres, but not the centromeres, are clustered at the position of the SPB. This change in the position of the chromosome within the nucleus occurs in human cells too, and it was shown that this mechanism is vital in the production of reproductive cells such as sperm and ova. Our series of research reports into this mechanism was published in top international journals including Science and Cell[2]–[4].

This cell imaging technology using the multicolor 3D fluorescence microscopy system is a powerful research tool, but it alone was not enough to examine the internal structures of cells. Examining the lipid membrane in

particular required development of new methods. The live CLEM method (Live CLEM: Live-cell imaging associated Correlative Light and Electron Microscopy) was developed to overcome this problem. In this method, a live cell is first observed over time using the multicolor fluorescence microscopy system mentioned above, and then this cell is chemically fixed and observed under an electron microscope (Fig. 2A). This method attracted a great deal of interest as an imaging method that combined the merits of fluorescence microscopy (molecule specific images of live cells) and electron microscopy (super high resolution enabling visualization of cell structures), and the results we obtained were published in top international journals[5][6].

While the development of imaging technology has been very successful, research has yet to be carried out into capturing direct images of changes in DNA switches within live cells. Developing a method of capturing high-resolution images of localized structures of DNA in a living cell has now become the pressing issue. To tackle this problem we are currently using structured illumination to develop 3D structured illumination microscopy (3D-SIM) and software[7]. Using this method has allowed us to clearly observe the structure of chromosome DNA (Fig. 2B). This type of imaging technology is one of the most important fundamental technologies, and it will become a founding technology of not only bio-ICT research, but also cellular and sub-cellular dependent bio-research.

2.3 Technology for measuring the amount of information read from DNA

In order to measure the amount of genetic information read from DNA by organisms, we established a DNA microarray technology. This technology measures the gene expression level of each of the genes in a cell (around 23,000 genes in human beings and 5,000 genes in fission yeast) of the target organism. In this method, DNA is fixed onto a confined area on a glass substrate, and the level of bonding with RNA (mRNA) is measured to ascertain the amount of information that has been read. Figure 3 shows the results of examining the on-off state of around 5,000 genes in fission yeast. Green indicates the switch is turned off, and red indicates the switch is turned on. The accuracy of our system is extremely high. We analyzed gene expression in fission yeast using this DNA microarray, and clarified the mechanism behind how the spatial arrangement of the DNA within the nucleus is determined, and the importance of the centromere structure. These results were published in Cell, Nature, Science and other leading journals[4]–[9].

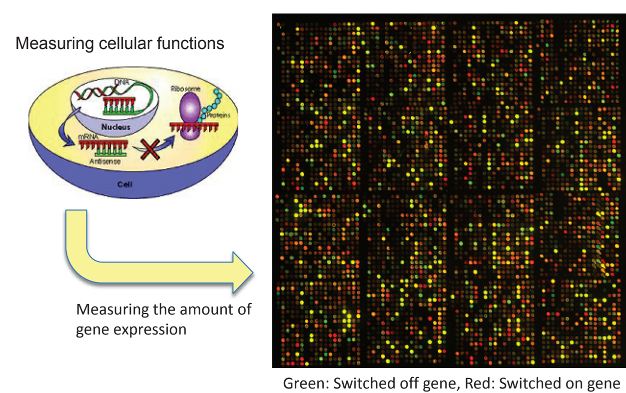

Fig. 3 Measuring gene expression using DNA microarray
On the left is a schematic diagram of a cell. On the right is actual data from an analysis of the switching on and off of 5,000 genes in fission yeast cells.

3 Developing interface technology to connect organisms with abiotic materials

Developing bio-ICT with cells will require the development of interfaces to connect communication media with cells. In an initiative to address this issue, we are studying the response of cells to having artificial material implanted in them. For this, we are currently using plastic beads (with a diameter of around 3 micrometers), which cannot be broken down by the cells. We are attaching DNA and proteins that are highly compatible with the cells onto the surface of the plastic beads and then introducing them into the cells. We know from past research that such beads are taken into the cells via the cells' ability to "swallow substances." The enveloping membrane is then torn open, releasing the beads inside the cells. However, objects that enter the cell from outside are regarded as foreign matter and trigger a response to break down or remove such material known as autophagy in which foreign substances are "eaten up"[10]. Thus, when the beads are released inside the cells, it triggers an autophagic response and the beads are swallowed up by another type of membrane, which then tries to break them down. Because we need to take this response into account when building interfaces between cells and artificial materials, an understanding of this phenomenon is vital for the future development of bio-ICT with cells.

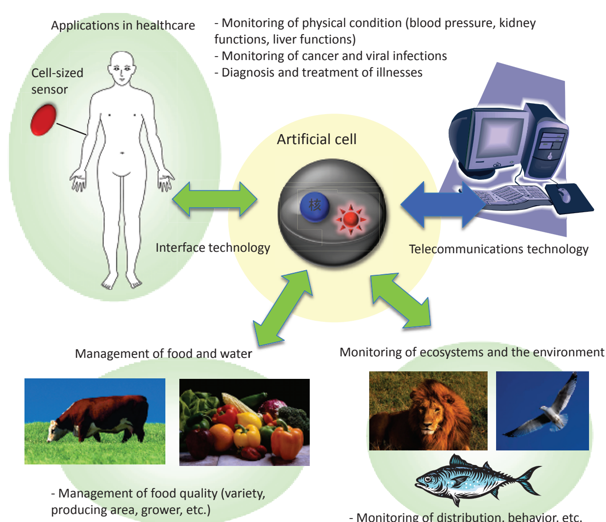

Fig. 4 Future ICT made possible by artificial cells

4 Developing ICT using cells

To use cells in ICT, the two most important issues to be addressed are (i) elucidating the parts, devices and systems of the cell in order to gain an understanding of how these extraordinary information processing machines function and (ii) developing a cell-ICT interface, as mentioned above. As part of a global trend, initiatives to build artificial cells are picking up momentum both domestically and overseas. Recent research has succeeded in artificially modifying cell functions and building parts of cell structures inside test tubes. With these advances, research into making use of interfaces between cells and artificial materials is advancing to a stage where it is on the verge of becoming reality. Figure 4 shows a proposed bio-ICT of the future using an artificial cell. Making an artificial cell customized to the needs of its objective will have applications in healthcare, food management, and a variety of other fields.

Acknowledgments

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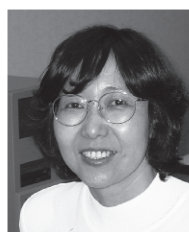

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