Cruising Inside Cells

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The behavior of biochemical molecules moving around in cells makes me think of a school of whales wandering in the ocean, captured by the Argus system on an artificial satellite. When bringing a whale back into the sea with a transmitter on its dorsal fin, every staff member hopes that it will return safely to a school of its species. A transmitter is now minute in size, but it was not this way before. There used to be some concern that a whale fitted with a transmitter could be given the cold shoulder and thus ostracized by other whales for "wearing something annoying." How is whales' wandering related to the tide or a school of small fish? What kind of interaction is there among different species of whales? We human beings have attempted to fully understand this fellow creature in the sea both during and since the age of whale fishing.

In a cell imaging experiment, a fluorescent probe replaces a transmitter. We label a fluorescent probe on a specific region of a biological molecule and bring it back into a cell. We can then visualize how the biological molecule behaves in response to external stimulation. Since fluorescence is a physical phenomenon, we can extract various kinds of information by making full use of its characteristics. For example, the excited energy of a fluorescent molecule donor (energy donor) transfers to an acceptor (energy receptor) relative to the distance and orientation between the donor and acceptor. This phenomenon (fluorescence resonance energy transfer) can be used to identify interactions between biological molecules or structural changes in biological molecules. In addition, we can apply all other characteristics of fluorescence such as polarization, quenching, photobleaching, and photoisomerization in experimentation.

Specific external stimuli cause specific cascade reactions inside cells, so that cell phenomena like differentiation, migration, and division will result. Many molecules involved in intracellular signal transduction have been identified along with their hierarchical relations. It is not uncommon for us to see a signal transduction diagram in which arrows are used to link molecules to show enzyme reactions and intermolecular interactions.

However, to obtain an all-embracing understanding of a signal transduction system, the diagram must contain three axes in space and the time base, because all events are controlled ingeniously in space and time. This scale over time and space is ignored in biochemical approaches in which electrophoresis is applied to a specimen prepared by grinding millions of cells — which means that the resulting understanding is far from satisfactory. There is a need to employ the so-called real-time and single-cell imaging technique, which allows us to observe events in each living cell in real time.

A feedback mechanism from lower to higher hierarchy acts on the molecular network of a signal transduction system. Also, it involves interaction with other transduction systems. As a result, a biological phenomenon may sometimes react unpredictably to a scientist's arbitrary

action. For example, even in an experiment to excessively generate or eliminate specific molecular species, it is important to visualize their behavior not only downstream but also in the entire transduction system. We therefore aim at developing an imaging technique extravagant enough to ascertain when, where, and to what extent (i.e. quantitatively) various events take place inside cells. To describe the post-genome project, it is important to attempt to increase parameters that allow for simultaneous observation and are designed to describe intracellular signal transduction systems, rather than just setting holism against the theory of element reduction.

Cruising inside cells in a supermicro corps, gliding down in a microtubule like a roller coaster, pushing our ways through a jungle of chromatin while hoisting a flag of nuclear localization signal — we are reminded to retain a playful and adventurous perspective at all times. What matters is mobilizing all capabilities of science and giving full play to our imagination. We believe that such serendipitous findings can arise out of a sportive mind, a frame of mind that prevails when enjoying whale-watching.

Keywords:
Real-time and single-cell imaging: Observing events in each living cell in real time.

Fluorescence resonance energy transfer: Transfer of excited energy from a donor to an acceptor fluorescent molecule.