Cellular research: the past is the key to unlocking the present, and the present is the key to understanding the past

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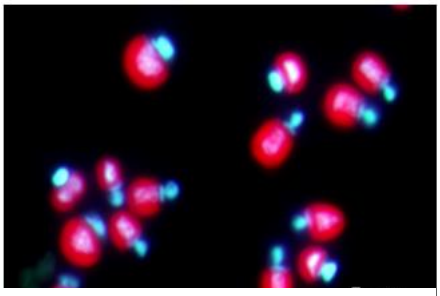
Where we came from is a question we all have. Compared to the origin of the universe and the origin of the earth, there are many things we do not know about the origin and early evolution of life, even though these are our direct roots. I have been working from the viewpoint that the key to unlocking the mysteries of evolution may lie in the mechanisms of the cell as we know it today.

The minimum unit of life on earth is the cell. There are two types of cells: prokaryotic cells, such as bacteria that do not have a cell nucleus, and eukaryotic cells that contain cell organelles (organelles) such as the nucleus and mitochondria inside the cell, both of which carry out life activities according to the central dogma centered on the DNA genome. Various theories have been proposed regarding the origin and evolution of these cells, but the current prevailing theory is that life originated on earth as prokaryotic cells, and eukaryotic cells evolved through their symbiosis. However, it is still unclear how prokaryotic cells emerged from non-living matter and how eukaryotic cells evolved from prokaryotic cells. Knowing the origin of cells leads to understanding their basic functions and mechanisms. Conversely, a deeper understanding of current cellular mechanisms should allow us to infer cell evolution. However, our knowledge has not yet reached that level, and solving this mystery is one of the most important challenges of modern biology.

Our approach to these mysteries has been to study primitive microorganisms. When we think of eukaryotic cells, we think of animal and plant cells. However, these cells are very complex, and it is advantageous to use simpler microorganisms to study their basic mechanisms. The advantage of microbial research can be recognized from the fact that Dr. Ohsumi's discovery of autophagy was established in yeast research, and the basics of biology, central dogma, were established in bacterial and phage studies. From this perspective, we are conducting our studying using the unicellular algae *Cyanidioschyzon merolae*. Among eukaryotic cell organelles, mitochondria and chloroplasts have their own DNA genome and are thought to be descendants of bacteria that symbiotically coexisted within the cell in prehistoric times. Since cellular symbiosis is an event closely related to the origin of eukaryotic cells and the subsequent origin of plant cells, clarification of how these symbionts "live" in the present-day cells will surely provide



Primitive model eukaryotic cell *Cyanidioschyzon*

clues to the origin and early evolution of eukaryotic cells.

A *Cyanidioschyzon* cell contains one mitochondrion and one chloroplast; each multiplies by repeating a replication cycle consisting of DNA replication and division. Of course, there is also a cell cycle centered on the nucleus. Therefore, in a *Cyanidioschyzon* cell, the three independent replication cycles are coordinated under a certain relationship and function as a single cell. The cell cycle begins with nuclear DNA replication, but in the replication cycle of the *Cyanidioschyzon* cell, mitochondrial and chloroplast DNA replication occurs before nuclear DNA replication. We have investigated the molecular mechanism that determines the order of DNA replication in detail and discovered how nuclear DNA replication awaits organelle DNA replication. Until organelle DNA replication occurs, nuclear DNA is not replicated because the cyclin proteins necessary for nuclear DNA replication are actively degraded. When organelle DNA replication occurs, a signal molecule (MgProto) is released from the chloroplast into the cytoplasm, inhibiting cyclin degradation and inducing nuclear DNA replication. Chloroplasts are derived from photosynthetic bacteria (cyanobacteria), which cannot grow in the dark. When cells divide under such conditions, the proportion of chloroplast-free cells gradually increases. This very simple trick was probably created in the early evolution of chloroplasts to stabilize the symbiosis by waiting for the cell cycle to progress in the dark. And as a result, we could assume that plant cells evolved not to proliferate in the dark.

As described above, studying the relationship between the nucleus and symbiosis-derived organelles will lead to a better understanding of the basic mechanisms of the present eukaryotic cell and provide various insights into the origin of the eukaryotic cell. Going back even further, the origin of prokaryotic cells should have been the very origin of life, but imagining that process is even more difficult than considering the origin of eukaryotic cells. However, complex cells such as today's bacteria did not arise suddenly but, in fact, evolved step by step from simpler systems. The key to unlocking this path may be found in today's cells.

Related Research Results

Kan Tanaka and Mitsumasa Hanaoka (2013) Hypothesis and theory: The early days of plastid retrograde signaling with respect to replication and transcription. *Front. Plant Physiol.* 3, 301.

Yuki Kobayashi, Sousuke Imamura, Mitsumasa Hanaoka and Kan Tanaka (2011) A tetrapyrrole-regulated ubiquitin ligase controls algal nuclear DNA replication. *Nature Cell Biol.* 13, 483-487.

Yuki Kobayashi, Yu Kanesaki, Ayumi Tanaka, Haruko Kuroiwa, Tsuneyoshi Kuroiwa and Kan Tanaka (2009) Tetrapyrrole signal as a cell cycle coordinator from organelle to nuclear DNA replication in plant cells. *Proc. Natl. Acad. Sci. USA* 106, 803-807.