Division of Developmental Regulation

Cell Maintenance

The Rad18 protein, a built-in survival instinct Investigating the control panel of this gene to discover the mechanisms for prevention of carcinogenesis

Our DNA is constantly being damaged.
The reason why we can survive even with such damages in DNA is that there are mechanisms by which the replication of damaged DNA is controlled.
Dr. Tateishi aims to elucidate DNA replication mechanisms, raising expectations for significantly advancing research on cancer prevention and treatment for accelerated aging disorders.

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Profile

Obtained Bachelor's degree from Faculty of Science, Shizuoka University.
Received a Ph.D. from Graduate School of Science, Osaka University.
1990 Assistant professor, Institute for Medical Genetics, Kumamoto University Medical School.
2000 Assistant professor, Division of Organogenesis, Institute of Molecular Embryology and Genetics.
2003 Senior assistant professor, Institute of Molecular Embryology and Genetics.

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Rad18: always working in the interests of the living system as a whole

Our DNA is constantly being damaged by UV light irradiation and other sources. If DNA replication occurs without that damage being repaired, mutagenesis and replication fork collapse may occur more readily, leading to carcinogenesis and cellular death. For this reasons, humans come pre-programmed with a system to ensure that DNA is not replicated until the damage has been fully repaired. There are, however, some cases in which replication continues without complete repairing of the damages. Dr. Tateishi's research aims to clarify the complexities of DNA replication mechanisms. He focuses in particular on a protein called "Rad18."

"We know that, if something should occur to the human cells that causes a dangerous situation, one in which many genes may become damaged, Rad18 works to send signals to replicate DNA nevertheless, even if the DNA is damaged". In other words, in critical situations in which significant damage has occurred, Rad18 forces the cells to replicate DNA despite the damage, and in spite of the inherent risk of the mutations that may occur as a consequence of such replication. It functions to prioritize life, survival, above all else, by protecting the all-important cells. "This protein works to protect the interests, namely the survival, of the living system as a whole. It's an intriguing mechanism," says Dr. Tateishi.

Promoting cellular aging, preventing carcinogenesis

This research is closely linked to studies into cancer prevention and treatment.

We are beginning to understand how active aging of the cells functions to prevent those cells from becoming cancerous. "Aging has a bad image, but actually it plays a very important function in the living body," explains Dr. Tateishi. The impairment of DNA replication can be a factor in cell aging. "At the same time, cell aging may also be provoked if there is a lack of Rad18 activity. So we need to harness this; cancerous cells aggressively replicate their DNA, which makes them vulnerable to the stress caused by replication. If we can downregulate the expression of Rad18, then it may be possible to promote cell aging and thereby halt the progress of the cell carcinogenesis." A Rad18 knockout mouse line showed a decrease in testes (reproductive organ) weight, suggesting decreased fertility. "What this suggests is that there is a particular concentration of cell aging within the germ cells, in which DNA replication is highly active." Here, Dr. Tateishi has found that it is possible, to a certain extent, to prevent carcinogenesis in mouse lines susceptible to cancer by knocking out the Rad18 gene.

Expectations for discovery and treatment for accelerated aging disorders

Accelerated aging disorders occur when DNA repair mechanism fails to function adequately, meaning that damage to DNA is not properly repaired. Cell aging, supposed to protect us from cell carcinogenesis, is consequently abnormally accelerated. They do not start to age upon growing old; rather, children with these disorders will begin to show the symptoms of old age before they reach age ten. In recent years, Dr. Tateishi has been working on a study focusing on developing a treatment for Cockayne syndrome, one type of accelerated aging disease. Working as part of a team under the jurisdiction of the Japanese Ministry of Health, Labour and Welfare, he is conducting work designed to translate the findings of research on DNA replication mechanisms into possible clinical therapies for this disease.

"In this research program, we derive fibroblasts from patients indicating signs of ***Cockayne syndrome***, use them cells, and try to control aging by adding inhibitors for it. Then we look to see whether there is any effect." There are a number of different kinds of accelerated aging disorders; research looking at the potential impact of drugs on such disorders is a step-by-step process. Researchers must first identify a clear target, then see what happens when we treat the cells with a certain inhibitor that might downregulate a certain function of a certain gene. "Developing a new drug that works on an intractable disease is catering to a very limited market, so it's hard for drug companies—private industry, in other words—to commit to this kind of research," notes Dr. Tateishi. "But that's exactly why we need to be working on this. It's the role of universities to make steady efforts to find effective one among the commonly used drugs.