How Cancer Cells Loose Their (Circadian) Rhythm

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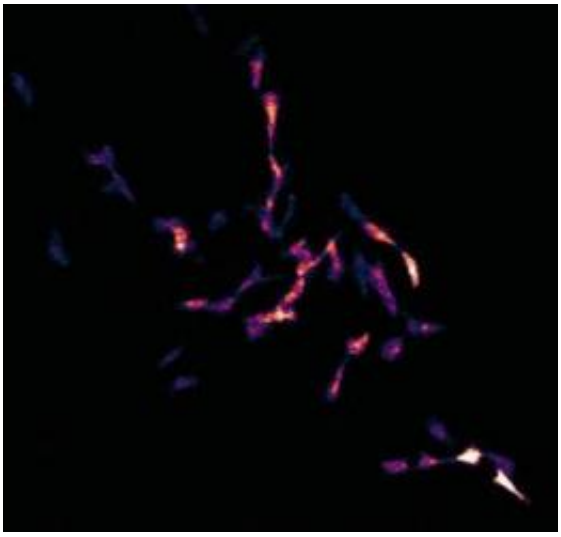

An image from the customized system that Shin Yamazaki has developed for tracking the process of cell division in mammalian cells. The system involves inserting the genes for a luminescent enzyme into a strain of mammalian cells in such a fashion that the enzyme is released when the cells are dividing. This allows the researchers to continuously track the rate of cell division over long periods of time by photographing the changes in luminescence. Credit: Yamazaki Laboratory

Immortality and uncontrolled cell division are the fundamental differences between cancer cells and normal cells.

A widely held explanation for these differences is that the biological

clocks in cancer cells are damaged and can't regulate cell division in the fashion that they do in normal cells.

This assumption is challenged by the results of the first experiment that has continuously monitored variations in the rate of cell division of cultured mammalian cells for extended periods. The results are reported this week in a paper published in the online Early Edition of the Proceedings of the National Academy of Sciences.

The experiment discovered that one line of immortal cells have functioning biological clocks but their internal clocks have no effect on the rate at which they divide and grow. (Immortal cells have the same basic properties as cancer cells but are created in the laboratory where they are used for a wide variety of purposes.)

"The current assumption has been that the biological clocks in cancer cells have been disabled," says Julie Pendergast, a research associate who participated in the study. "We determined that the immortalized cells in our experiment had functioning biological clocks but these clocks don't control the process of cell division. That is the paradigm shifting aspect of our study."

If confirmed by follow-up studies, this insight could aid in the development of new cancer therapies.

"This strengthens the possibility that the biological clock pathway could be an effective target for anti-cancer drugs," says Shin Yamazaki, the research professor of biological sciences at Vanderbilt who directed the project. "For example, if a drug could be found that restores the control of the biological clock over cancer cell division, it could reduce tumor growth."

Biologists have observed that cell division in normal cells in species

ranging from unicellular organisms to humans peaks at specific times of the day and consider this as indirect evidence that the process is regulated by their internal biological clocks. Cells in the human mouth, for example, tend to divide in the evening, just before nightfall.

"There is a general evolutionary explanation for this," says research associate Julie Pendergast who participated in the study. "Ultraviolet light is one of the primary causes of mutations. Cells are particularly vulnerable to mutations during cell division. So organisms with cells that divide at night have a selective advantage."

In addition, there has been a considerable amount of indirect evidence that mitosis (division) in cancer cells is not under 24-hour control. For example, "experiments have found that cells turn cancerous when certain circadian clock genes have been knocked out," says Yamazaki. The results of other experiments that have periodically sampled cancer cell division rates also support this possibility.

Yamazaki designed and built a special system to monitor cell division in real time. He and his colleagues designed a special "reporter" molecule incorporating a gene that produces an enzyme that makes green light. They figured out how to insert this reporter into a cell's genome so that it produces the luminescent enzyme when the cell divides. This allows them to use a camera to continuously measure variations in the rate of cell division over long periods of time.

For the current experiment, the researchers inserted their special reporter into immortalized rat fibroblasts formed from connective tissue taken from rats. They selected this cell line because it was known to have working circadian clocks.

They have obtained consistent results in preliminary studies of lung cancer cells.

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