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Findings could advance therapies in both fields

BIOTECH: Cancer, stem cells linked in Salk study

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SAN DIEGO ---- A widely accepted theory of how cancer arises has been challenged by a study led by scientists at the Salk Institute.

The findings may shed new light on strategies to fight cancer, as well as how to increase the efficiency of "reprogramming" normal cells to become embryonic stem cells for use in treating diseases.

The research links cancer development with difficulties in the new technology of reprogramming normal cells into becoming like embryonic stem cells, said Salk professor Juan-Carlos Izpisua Belmonte, who led the study. An article about the study's findings was published online Sunday in the science journal Nature.

About two years ago, scientists found that normal cells can be turned into cells apparently identical to embryonic stem cells. This reprogramming could overcome the ethical objections to getting these cells from human embryos. But the process has safety concerns, and it is inefficient.

A cancer-preventing gene called p53 is the link between the difficulties in reprogramming and cancer, according to the study.

Nearly all cancers have a disabled p53 gene. The gene causes cells that have experienced major genetic damage, which puts them at high risk of turning malignant, to self-destruct. While several mutated genes are implicated in cancer, p53 appears to be the most important one. Because of its protective role, p53 has been dubbed "guardian of the genome,"

When the p53 gene is removed, normal cells can be reprogrammed into stem cells with a tenfold greater success rate, the study found.

If the link is confirmed by other researchers, it would undermine a popular hypothesis that cancers arise from "cancer stem cells," caused by genetic changes in stem cells, Belmonte said. Instead, he suggested, cancer could begin when normal cells spontaneously reprogram themselves, for reasons yet unknown, beginning the process that results in a cancerous tumor.

"If we know the genes and the mechanisms involved in reprogramming ... I'm sure we're going to understand much better about cancer," Belmonte said.

Cells must have safeguards in place to prevent reprogramming, or it would occur frequently, Belmonte said. A better understanding of how to cause reprogramming could provide clues about how this might arise spontaneously. And that knowledge could be useful in developing cancer-fighting therapies, he said.

Human embryonic stem cells are the "ancestral" cells that turn into nearly all the specialized cells in the human body, such as for the liver or skin.

They are being studied as possible treatments for diseases and injuries. But they are taken from days-old embryos, which is morally objectionable to many who consider the embryos to be human individuals.

Producing embryonic stem cells from normal cells by reprogramming is morally acceptable, because the reprogrammed cells cannot produce whole embryos by themselves, said the Rev. Tad Pacholczyk, director of education at the National Catholic Bioethics Center in Philadelphia. The center advocates official Catholic teaching.

However, only a very small percentage of the cells treated with the reprogramming methods actually turn into embryonic-like stem cells. And most techniques use four genes, including two "oncogenes," genes known to be involved in cancer development, inserted by a virus. So scientists are trying to develop more effective methods that don't use oncogenes or

viruses.

That's where the p53 gene can help, Belmonte said: Removing the p53 gene eliminated the need for the two oncogenes, so only two genes were needed for reprogramming.

"We are reducing, little by little, the number of factors needed for reprogramming," Belmonte said.

Belmonte said it should be possible to temporarily block the p53 gene when reprogramming cells, increasing the effectiveness of reprogramming without increasing the risk the cells will become cancerous.

"We are starting to do screening to find chemicals to block p53," Belmonte said.

Belmonte said article co-author Geoffrey M. Wahl, a cancer specialist and also a Salk professor, helped him understand the implications for cancer research.

Other co-authors included Teruhisa Kawamura, Jotaro Suzuki and Yunyuan V. Wang; all of the Salk. The others were Sergio Menendez, Laura Batlle and Angel Raya; all of the Center of Regenerative Medicine in Barcelona, Spain.

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