Scientists discover mechanism that turns mutant cells into aggressive cancers

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Eros Lazzerini Denchi of The Scripps Research Institute co-led the study with Agnel Sfeir of New York University School of Medicine. Credit: The Scripps Research Institute.

Scientists at The Scripps Research Institute (TSRI) have caught a cancer-causing mutation in the act.

A new study shows how a gene mutation found in several human cancers, including leukemia, gliomas and melanoma, promotes the growth of aggressive tumors.

"We've found the mechanism through which this mutation leads to a scrambling of the genome," said TSRI Associate Professor Eros Lazzerini Denchi, who co-led the study with Agnel Sfeir of New York University (NYU) School of Medicine. "That's when you get really massive tumors."

The research, published May 26, 2016 by the journal *Cell Reports*, also suggests a possible way to kill these kinds of tumors by targeting an important enzyme.

A Puzzling Finding

The researchers investigated mutations in a gene that codes for the protein POT1. This protein normally forms a protective cap around the ends of chromosomes (called telomeres), stopping cell machinery from mistakenly damaging the DNA there and causing harmful mutations.

POT1 is so critical that cells without functional POT1 would rather die than pass on POT1 mutations. Stress in these cells leads to the activation of an enzyme, called ATR, that triggers programmed cell death.

Knowing this, scientists in recent years were surprised to find recurrent mutations affecting POT1 in several human cancers, including leukemia and melanoma.

"Somehow those cells found a way to survive—and thrive," said Lazzerini Denchi. "We thought that if we could understand how that happens, maybe we could find a way to kills those cells."

It Takes Two to Tango

Using a mouse model, the researchers found that mutations in POT1 lead to cancer when combined with a mutation in a gene called *p53*.

"The cells no longer have the mechanism for dying, and mice develop really aggressive thymic lymphomas," said Lazzerini Denchi.

P53, a well-known tumor suppressor gene, is a cunning accomplice. When mutated, it overrides the protective cell death response initiated by ATR. Then, without POT1 creating a protective cap, the chromosomes are fused together and the DNA is rearranged, driving the accumulation of even more mutations. These mutant cells go on to proliferate and become aggressive tumors.

The findings led the team to consider a new strategy for killing these tumors.

Scientists know that all cells—even cancer cells—will die if they have no ATR. Since tumors with mutant POT1 already have low ATR levels, the researchers think a medicine that knocks out the remaining ATR could kill tumors without affecting healthy cells. "This study shows that by looking at basic biological questions, we can potentially find new ways to treat cancer," said Lazzerini Denchi.

The researchers plan to investigate this new therapeutic approach in future studies.

Provided by The Scripps Research Institute

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