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'Master controller' behind DNA structure reorganization during senescence identified

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Senescence, a phenomenon in which cells cease to divide and grow, can be caused by everything from natural DNA damage to treatment with chemotherapy. However, several mechanisms allow for cells to bypass senescence and grow out of control, eventually becoming cancerous. Now, scientists at The Wistar Institute have identified how a specific variant of a key protein complex found in human cells called condensin can reorganize a cell's genetic architecture in such a way as to promote senescence, making it an important facilitator in a cell's anticancer ability.

The findings were published online by the journal *Cell Cycle*.

This novel mechanism by which condensin is able to drive senescence

could give researchers clues on important targets for future therapies designed to halt the progression of cancer.

Each of our cells contains enough DNA that, if stretched out in a line, would total about six feet in length. Condensin helps to compact all of that essential genetic information into something that can fit into a microscopic cell to enable the formation of chromosomes and preserve the DNA when a cell divides. Many eukaryotic cells - cells that have an organized nucleus - have two types of condensin, each of which has its own specific subunits that dictate its activity. In his lab, Ken-ichi Noma, Ph.D., associate professor in Wistar's Gene Expression and Regulation Program, has studied how condensin II complexes are able to modulate gene expression in a variety of organisms, including humans.

"Because of its role in the regulation of gene expression, we knew that condensin II likely played an important role in genome organization and architecture," said Noma, who is lead author of this study. "However, we did not fully understand the connection it might have with senescence. With these latest findings, we show that one specific subunit in condensin II leads to cellular senescence, thus revealing important information about the anti-cancer activity of our cells."

In this study, Noma and his colleagues looked at subunits of the condensin II complex. When comparing the condensin II complex of a normal cell line with those of three cancerous cell lines, they found that two different sizes of a particular subunit existed in the normal cell line: a full length version of the antibody hCAP-H2 and a shortened version called hCAP-H2ΔN. However, only the full length version existed in the cancer cell lines. When restimulation assays were performed, the researchers were able to confirm that the full length version of hCAP-H2 was highly involved in mitosis, an essential process that enables cells to keep growing, thus confirming the role they play in cancerous cells.

However, they discovered that both versions of hCAP-H2 play an important role in senescence, with the ΔN more likely participating in the induction of senescence. First, the researchers observed that the overexpression of both forms of hCAP-H2 induced senescence. The researchers then further observed that the expression of the ΔN variant increased during Ras-induced senescence. Ras is a cancer causing gene, or oncogene, which would normally be associated with abnormal cell growth and proliferation. However, depending on the cellular environment, activated Ras can act as a tumor suppressor by causing senescence.

"Condensin II complex is part of an interesting protein complex contributing to a cell nucleus environment that antagonizes proliferation," said Dario C. Altieri, M.D., president and CEO of the Wistar Institute and director of The Wistar Institute Cancer Center. "Through Noma's work, we now understand its molecular function in cellular senescence, and it may be possible that this pathway plays an important first line of defense against the emergence of tumors in humans, activating an irreversible senescence program in the malignant cell."

Provided by The Wistar Institute