BREAKTHROUGHS

TRACING DNA DELETIONS MAY LEAD TO NEW CANCER THERAPIES

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In an effort to understand cancer on a cellular level, a team of City of Hope researchers have been examining DNA deletions and their role in the disease. Recently, they discovered new information that could lead to better therapeutics.

A central step in the development of cancer is loss of genetic information, which can include the removal of a large segment of chromosomal DNA, called deletions, explained Jeremy Stark, Ph.D. a professor in City of Hope's Department of Cancer Genetics and Epigenetics, whose lab seeks to understand the factors and pathways that influence mammalian genome instability, with a focus on cancer-associated chromosomal rearrangements.

Jeremy Stark, Ph.D.

One way that deletions can form is due to a break in DNA that is repaired using similar patterns of nucleic acids (called homologous repeat elements) that exist on both sides of the break. The chromosome is fixed by this repair, but the DNA between the repeat elements, along with one of the repeats, is lost or deleted. In cancer cells, these deletions can involve repeat elements that are relatively far apart. Previously, it had been unclear how close the break in DNA needed to be to the repeats in order to cause these deletions.

"Using a mouse cell culture model, we found that a break can indeed be relatively far from a repeat and still induce these deletions," said Stark, who was the corresponding author on a recent paper outlining these findings. "Using our experimental system, we have begun to understand the cellular pathways that influence whether a break will cause large deletions that use repeats."

The paper, "Repeat-mediated deletions can be induced by a chromosomal break far from a repeat, but multiple pathways suppress such rearrangements," by Carlos Mendez-Dorantes and Ragini Bhargava, both graduate students at the Irell & Manella Graduate School of Biological Sciences at City of Hope, and Stark was published in the April 10 issue of the journal *Genes and Development*

The next step for the research team is to conduct additional studies to help further their understanding the details of DNA repair pathways. This has relevance not only for understanding how cancer develops, but also for developing therapeutic methods, said Stark. And that's because many of the current approaches to treating cancer involve agents that actually cause DNA breaks.

"Some cancer cells have lost aspects of their ability to respond to DNA breaks, and hence could be more reliant on repair processes that use repeats for survival," said Stark, "Thus, understanding the pathways of DNA break repair is critical to develop therapeutic targets to improve cancer cell response to current agents that work by breaking DNA."

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