Textbooks on cells should be rewritten

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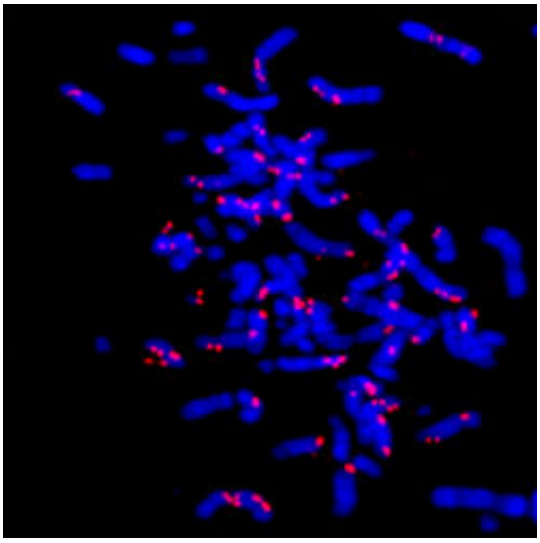

Ground-breaking new Danish research has shown that the current scientific description of the human cell cycle needs to be revised. These findings could also lead to the development of new therapeutic approaches to target an Achilles' heel in different types of cancers.

All science students learn how human cell division takes place. The copying or replication of the genome, the cell's DNA, has until now been believed only to take place during the so-called S-phase in the cell cycle. The new results show that this is not the case, because some regions of the genome are copied only after the cell enters the next crucial phase in the cell cycle called mitosis.

"It has radically altered our views and requires that the textbook view of the human cell cycle be revised", says Professor Ian Hickson, Director of the Centre for Chromosome Stability and affiliated with the Center for Healthy Aging.

The research project was funded by the Danish National Research Foundation and was just published in the international scientific journal *Nature*.

Fragile sites associated with cancer

This unusual pathway for copying of the DNA occurs at specific regions of the human genome called fragile sites, and during mitosis, chromosomes in these fragile areas have a tendency to break. The fragile sites are conserved across species and are frequently associated with undesirable genome rearrangements in connection with the development of cancer.

"We now know that these so-called 'chromosome breaks' are not actually broken, but instead comprise a region of DNA that is newly synthesized in mitosis. They appear broken because they are far less compacted than the rest of the chromosome," adds Professor Hickson.

Cancer cells utilize this unusual form of DNA replication because one of the side effects of the genetic changes that cause cancer is so-called 'replication stress'.

Curiosity and a chance observation

The scientists weren't specifically looking for this but fortunately they saw something very unusual when looking at human cancer cells under the microscope. "When we realized what was happening, it took us about

3 years to determine the mechanism underlying this phenomenon."

"All science students learn that DNA is replicated in S-phase. Our results show that this is not the case, because some regions are replicated only after the cell enters mitosis," he adds.

Achilles' heel of human cancers

The scientists already know of two proteins that are essential for this unusual pathway for DNA replication, but now aim to define the full 'toolbox' of factors that are required. They can then proceed with studies to identify chemical compounds that block the process. This would constitute the first stage in identifying potential new treatments for cancer.

"Although it has not yet been proven, it seems that the growth of many, or indeed most, cancers in humans is dependent on this process. Hence, the development of a reliable, therapeutic drugs strategy would likely have wide applicability in cancer therapy."

"Our aim is to generate results that will lead to the development of new approaches to treatments of various types of cancer," concludes Professor Hickson.

More information: Sheroy Minocherhomji et al. Replication stress activates DNA repair synthesis in mitosis, *Nature* (2015). DOI: 10.1038/nature16139

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