Press release

6 September, 2023

Discovery of an original DNA repair system, bringing new hope for the treatment of breast and ovarian cancer

Almost half of breast and ovarian cancers are connected to deficiencies in the biological systems that repair DNA breaks. Researchers from Institut Curie, Inserm and CEA reveal a hitherto unknown DNA repair mechanism involving a protein: Polϴ, which is able to act during cell division. Published in *Nature* on 6 September, 2023, their results pave the way for the development of new therapeutic targets for treating cancers, particularly breast and ovarian cancer.

Ultraviolet rays, alcohol, tobacco, genetic predisposition, spontaneous mutations... so many factors constantly damage our genome. Among these lesions, breaks that affect both DNA strands simultaneously are the most harmful. Our body is constantly repairing this damage through several repair systems, including homologous recombination. However, when these mechanisms fail (due to a genetic mutation, for example), they may cause cancer to occur. Also, the proven correlation between these homologous recombination deficiencies and the aggressiveness of cancers or their resistance to current chemotherapies underlines the pressing need for targeted cancer-fighting therapies.

A new major player in DNA repair: Polϴ

A few years ago, **a new player in DNA repair (polymerase theta or Polϴ) was identified as a therapeutic hope for treating these cancers[1].** The "Alternative DNA Repair Mechanisms in Human Cancers"[2] team headed by Dr. Raphaël Ceccaldi, Inserm researcher at Institut Curie, has just clarified **the mechanism for the action of this polymerase and the reason why this enzyme is vital to the development of breast and ovarian cancers.**

For the first time scientists have shown that Polϴ works where other DNA repair pathways do not. While it was believed that DNA repair was impossible during cell division (when DNA is extremely compacted), **the team from Institut Curie showed that Polϴ is active specifically during mitosis when the other contributors to repair were proven ineffective.**

> "Along with my team at Institut Curie, we looked closely at the mechanisms that the cell puts in place to repair its DNA, enabling cancer cells to survive. It is by understanding such mechanisms that we can build new options to thwart cancer", explains **Dr. Raphaël Ceccaldi, Inserm researcher and team leader at Institut Curie.** "Our discoveries on the role and functioning of polymerase theta in maintaining integrity of the genome gives us hope for new therapeutic strategies against cancer, particularly breast and ovarian cancer."

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[1] Ceccaldi R, Liu JC, Amunugama R, Hajdu I, Primack B, Petalcorin M, O'Connor KW, Konstantinopoulos PA, Elledge SJ, Boulton SJ, Yusufzai T, D'Andrea AD. **Homologous recombination (HR)-deficient tumors are hyper-dependent on POLQ-mediated repair.** *Nature.* 2015 Feb 12;518(7538):258-62.

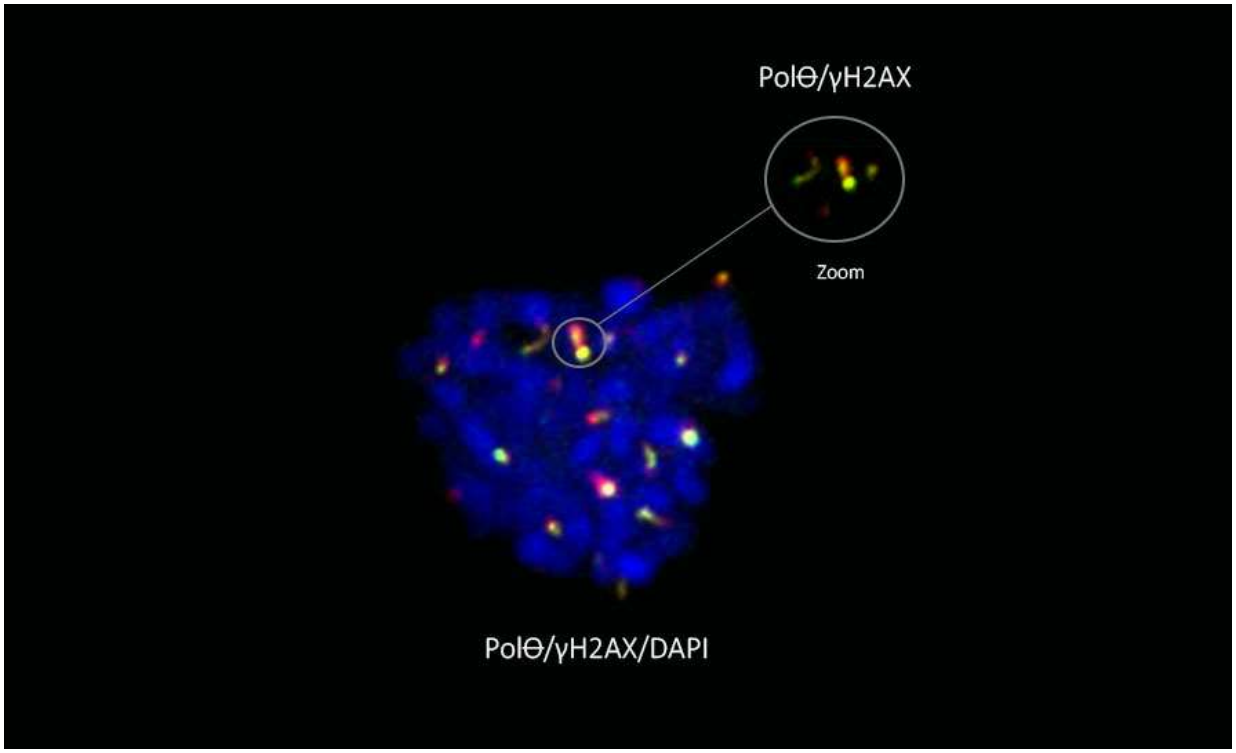
[2] Cancer, Heterogeneity, Instability and Plasticity unit - CHIP (U830, Institut Curie/Inserm)

Genome integrity highly preserved by Polϴ

Through a collaboration with the team of Dr. Sophie Zinn-Justin, researcher at the CEA (Laboratoire de Biologie Structurale et Radiobiologie), researchers went even further, showing that, in order to repair DNA, Polϴ had to be activated by an enzyme specifically present during cell division. In addition, **the mechanisms that enable this activation of Polϴ seem to have been extremely well-preserved throughout evolution. This suggests that they play an important role in maintaining the stability of the genome needed for development of eukaryotic organisms.**

A therapeutic hope for breast and ovarian cancer

The team of Dr. Raphaël Ceccaldi also discovered that **inhibiting Polϴ during cell division by mitosis prevents the proper repair of DNA and as a result leads to the death of cancer cells.** With almost half of breast and ovarian cancers showing DNA repair deficiencies by homologous recombination, this step therefore represents a milestone in the fight against these cancers. **Clarifying the molecular mechanisms governing the use and regulation of Polϴ could ultimately lead to the development of new therapeutic targets for treating these cancers.**



Polϴ (green) marks DNA breaks (γH2AX, red) in the mitotic chromosomes (DAPI, blue) – Scale 5µM

Reference:
Polθ is phosphorylated by PLK1 to repair double-strand breaks in mitosis.
Camille Gelot, Marton Tibor Kovacs, Simona Miron, Emilie Mylne, Alexis Haan, Liza Boeffard-Dosierre, Rania Ghouil, Tatiana Popova, Florent Dingli, Damarys Loew, Josée Guirouilh-Barbat, Elaine Del Nery, Sophie Zinn-Justin & Raphael Ceccaldi.
Nature – 6 September 2023 - https://www.nature.com/articles/s41586-023-06506-6

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Institut Curie, France's leading cancer center, combines an internationally-renowned research center with a cutting-edge hospital group, treating all types of cancer, including the rarest. Founded in 1909 by Marie Curie, Institut Curie has 3 sites (Paris, Saint-Cloud and Orsay) with over 3,700 researchers, physicians and health professionals working on its 3 missions: treatment, research and teaching. A foundation with public utility status, Institut Curie is authorized to accept donations and bequests, and thanks to the support of its donors, is able to accelerate discoveries and improve patient treatment and quality of life.
Find out more: www.curie.fr

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Founded in 1964, Inserm is a public scientific and technological institute which operates under the joint authority of the French Ministries of Health and Research. The institute is dedicated to biomedical research and human health, and is involved in the entire range of activities from the laboratory to the patient's bedside. It also partners with the most prestigious research institutions in the world that are committed to scientific challenges and progress in these fields.
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The CEA is tasked with guiding public decisions and providing the scientific and technical means that civil society (businesses and local authorities) needs to better manage major societal changes, such as the energy transition, digital transformation, future healthcare, defence and global security. Its mission is supported by 20,000 employees and 9 research centres equipped with major research facilities that provide an innovative environment conducive to academic and industrial partnerships in France, Europe and abroad.
For more information: www.cea.fr