How cancer cells repair DNA damage induced by next-generation radiotherapy

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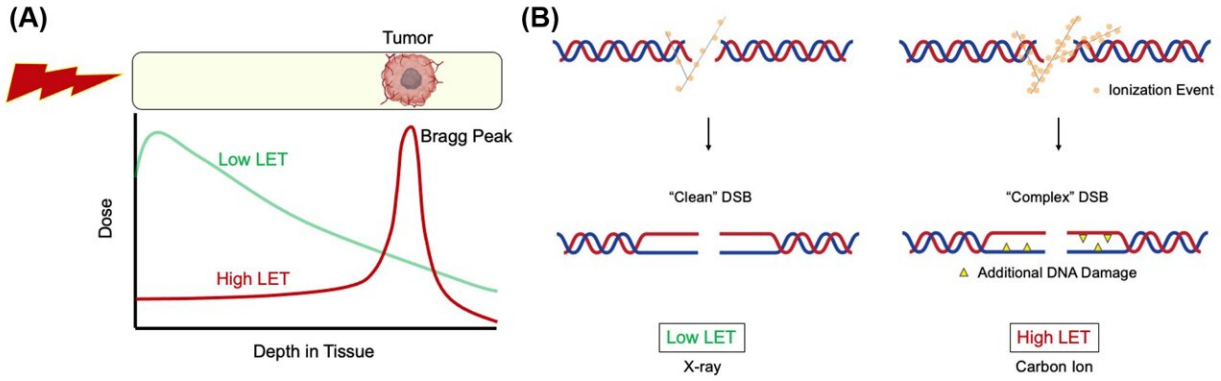


(A) Depth dose distribution for low LET X-rays and monoenergetic Bragg curve for high LET carbon ions. (B) Carbon ions produce more "complex" DSBs and X-rays produce relatively "clean" DSBs. Credit: *Nucleic Acids Research* (2023). DOI: 10.1093/nar/gkad076

A team of scientists led by Dr. Kei-ichi Takata from the Center for Genomic Integrity (CGI) within the Institute for Basic Science (IBS), has discovered a new type of DNA repair mechanism that cancer cells use to recover from next-generation cancer radiation therapy.

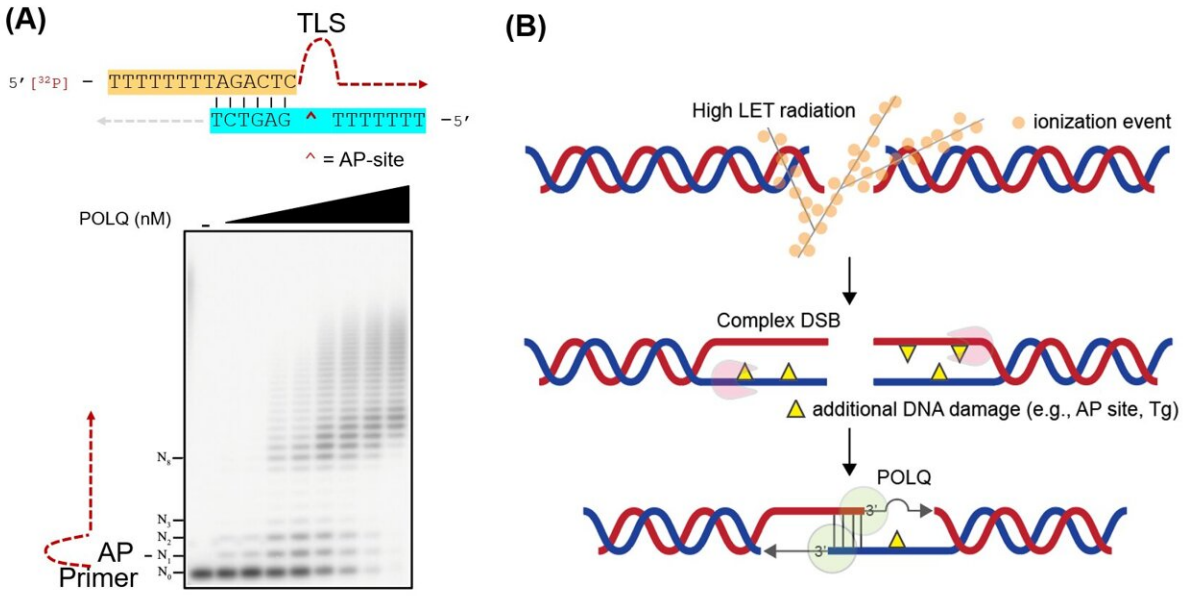
Ionizing radiation (IR) therapy is frequently used in the treatment of cancer and is believed to destroy cancer cells by inducing DNA breaks. The newest type of radiation therapy harnesses radiation produced by a particle accelerator, which consists of charged heavy particles such as

carbon ions. The particle accelerator accelerates the carbon ions to about 70% of the speed of light, which collides with and destroys the DNA of cancer cells.

These ions have a high linear energy transfer (LET) and release most of their energy within a short range, called the Bragg peak. The next-generation cancer radiotherapy works by focusing the Bragg peak on the tumor, which has the added benefit of minimizing damage to surrounding normal tissues compared to the commonly used low LET radiation such as gamma or X-rays.

Only a handful of medical facilities in the world currently possess the capability to deliver this next-generation radiation therapy, although more are hoped to be deployed in the future.

DNA lesions generated by heavy ion bombardment (high LET radiation) are more "complex" than those induced by traditional radiation therapy (low LET radiation). The former carries additional DNA damage such as apurinic/apyrimidinic (AP) site and thymine glycol (Tg) in close proximity to the double-strand breaks (DSB) sites, which is far more difficult to repair than ordinary DNA damage. As a result, the advanced therapy is more cytotoxic per unit dose than low LET radiation.



(A) POLQ is able to anneal two single-stranded DNA tails utilizing a short homology sequence and is able to bypass DNA damage. (B) A model of POLQ-mediated repair following high LET radiation. POLQ promotes synapsis formation of the two resected 3'-single-stranded DNA tails and efficiently bypasses DNA damage located on the tails. Credit: *Nucleic Acids Research* (2023). DOI: 10.1093/nar/gkad076

This makes next-generation radiation therapy a potent weapon against cancer cells. However, it has not been fully investigated how these high LET-induced lesions are processed in mammalian cells, as DNA damage from heavy ion bombardment is a process that seldom occurs in nature (e.g., higher chance in outer space). Figuring out the complex DSB repair mechanism is an attractive research interest since blocking the cancer cells' repair mechanism can allow the new radiation therapy to become even more effective.

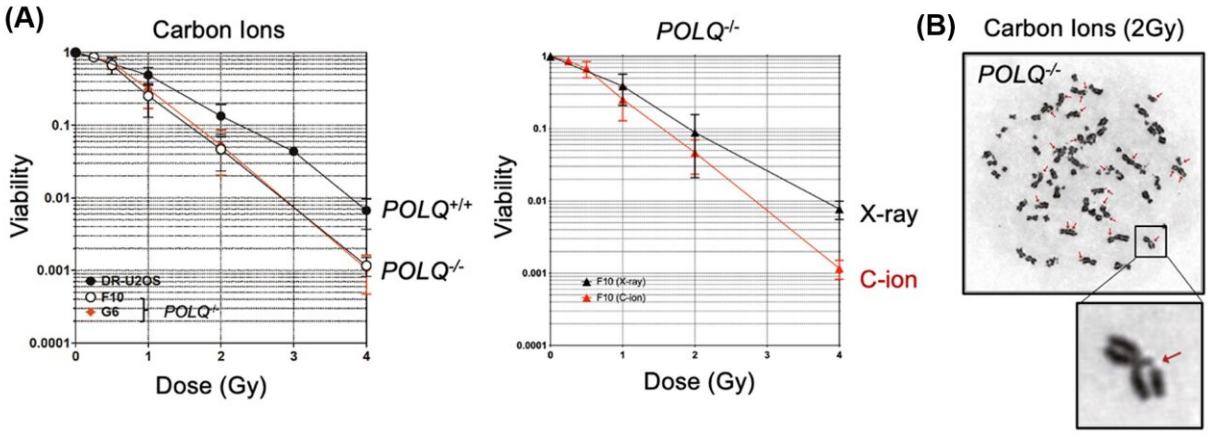
In order to conduct research, the IBS team visited the QST hospital in Japan to use the synchrotron named HIMAC (Heavy Ion Medical

Accelerator in Chiba), which has the ability to produce high LET radiation. A similar synchrotron has been installed at Yonsei University and another one is scheduled to be installed at Seoul National University Hospital in Kijang in 2027. Dr. Takata's research team intends to help establish a basic research program using these synchrotrons in South Korea to improve heavy ion therapy in cancer patients.

Dr. Takata's research team discovered that DNA polymerase θ (POLQ) is an important factor when repairing complex DSBs such as those caused by heavy-ion bombardment. POLQ is a unique DNA polymerase that is able to perform microhomology-mediated end-joining as well as translesion synthesis (TLS) across an abasic (AP) site and thymine glycol (Tg). This TLS activity was found to be the biologically significant factor that allows for complex DSB repair.

Sung Yubin, one of the joint first authors, explains, "We provided evidence that the TLS activity of POLQ plays a critical role in repairing hiLET-DSBs. We found that POLQ efficiently anneals and extends substrates mimicking complex DSBs."

The researchers also discovered that preventing the expression of POLQ in cancer cells greatly increased their vulnerability to the new radiation treatment.



(A) Effect of POLQ deletion on cell survival fraction after carbon ion or X-ray irradiation. (B) POLQ deletion increases chromatid breaks after carbon ion irradiation. Credit: *Nucleic Acids Research* (2023). DOI: 10.1093/nar/gkad076

"We demonstrated that genetic disruption of POLQ results in an increase of chromatid breaks and enhanced cellular sensitivity following treatment with high LET radiation," explains Mr. Yi Geunil, another joint first author.

The research team used biochemical techniques and Fluorescence Resonance Energy Transfer (FRET) to find out that POLQ protein can effectively repair synthetic DNA molecules that mimic complex DSB. This means that POLQ can be a possible new drug target to increase the cancer cells' vulnerability against complex radiation damage.

The single-molecule FRET assay system to monitor POLQ-mediated annealing and DNA extension was developed in collaboration with Prof. Kim Hajin and Mr. Kim Chanwoo at UNIST. Ms. Ra Jae Sun at IBS-CGI analyzed chromatid breaks induced by high LET radiation. Prof. Fujimori Akira and Mr. Hirakawa Hirokazu at QST, and Prof. Kato Takamitsu at Colorado State University helped conduct the experiments

with HIMAC.

Prof. Takata notes, "We are proud to announce the publication of our paper which was only possible through the great teamwork of everybody involved. Our findings provide new insights into the mechanisms of how hiLET-DSB is repaired in mammalian cells and further suggest that the inhibition of POLQ may augment the efficacy of heavy ion radiation therapy."

This work was published in *Nucleic Acids Research* on February 20, 2023.

More information: Geunil Yi et al, DNA polymerase θ-mediated repair of high LET radiation-induced complex DNA double-strand breaks, *Nucleic Acids Research* (2023). DOI: 10.1093/nar/gkad076

Provided by Institute for Basic Science

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