

Self-inflicted DNA damage drives cancer cell resistance to radiation therapy and buys them time to heal

Commonly used radiation therapy kills cancer cells by inflicting extensive DNA damage to the irradiated tissue. An international team including several researchers at the Institute of Molecular Genetics of the Czech Academy of Sciences in Prague (IMG), now shed light into an unexpected strategy of cancer cells to evade death by radiation in a study published in *Science*, one of the most prestigious scientific journals.

Naturally occurring DNA damage in human cells is efficiently remedied by a large number of DNA repair pathways. Yet this process takes time, and the addiction of cancer cells to rapid uncontrolled cell division renders them incapable of dealing with the level of DNA damage inflicted by high doses of radiation. As a result, radiation therapy efficiently kills tumor cells. Despite the success of the method, reoccurrence of tumors is still common. The mechanisms through which tumor cells manage to evade cell death after lethal doses of irradiation are not well understood, and hence resistance to RT remains a considerable challenge for effective clinical tumor control.

The team of scientists working in Denmark, Czech Republic, Sweden, Canada and Switzerland, coordinated by Claus Storgaard Sørensen at the Biotech Research and Innovation Centre, University of Copenhagen, Denmark, found that in response to radiation, tumor cells can activate endogenous nuclease CAD, an enzyme that breaks down nucleic acids, including DNA in the whole genome. While persistent DNA damage is generally bad news for the cell, here, the international research team found that by self-inflicting additional DNA breaks after the initial radiation-induced DNA damage, cancer cells efficiently suspend their program to divide, pause their cell cycle at the so-called G2 checkpoint before cell division and gain time to repair the remaining DNA damage.

This very surprising and somewhat counter-intuitive mechanism of how making more damage to themselves could increase the chance of irradiated tumor cells to survive, is explained by professor Jiri Bartek, one of the senior authors behind this project: *“While normal cells usually pause their division cycle at the so-called G1 phase control point, this mechanism is mostly defective in cancer cells. Therefore, the main option to prevent catastrophic cell division with broken chromosomes, which would kill the dividing cells, is to stay at the other, G2 phase checkpoint, just before the cells start dividing. The many CAD-made breaks ‘tell’ the tumor cells to wait until they repair the more dangerous DNA breaks caused by radiotherapy.”*

The strategy of adding targeted DNA breaks, as counterintuitive as it seems, improves the chance of cancer cells to survive lethal doses of radiation. They can be compared, for example, to soldiers in a war who injure themselves so that they cannot be sent into battle. What’s more, the authors found that this phenomenon was specific for cancer cells as loss of CAD activity rendered cancer cells, but not normal cells, vulnerable to radiation-induced damage. *“Indeed, this unexpected new mechanism suggests how cancer cells can adapt to DNA damage caused by radiation, thereby becoming more resistant to radiotherapy,”* explain Drs. Pavel Janscak and Vaclav Urban from IMG, who were involved in this discovery and are among the authors of this new *Science* article.

Collectively, the findings highlight a cancer-specific survival mechanism that could be targeted and exploited to enhance the tumor cells’ vulnerability to genotoxic cancer treatments. Indeed, the study also showed that experimental blocking of the CAD function made tumor cells (but not normal healthy cells) more sensitive to radiation, thereby suggesting how this new knowledge could be used to improve the outcome of radiotherapy in the future.

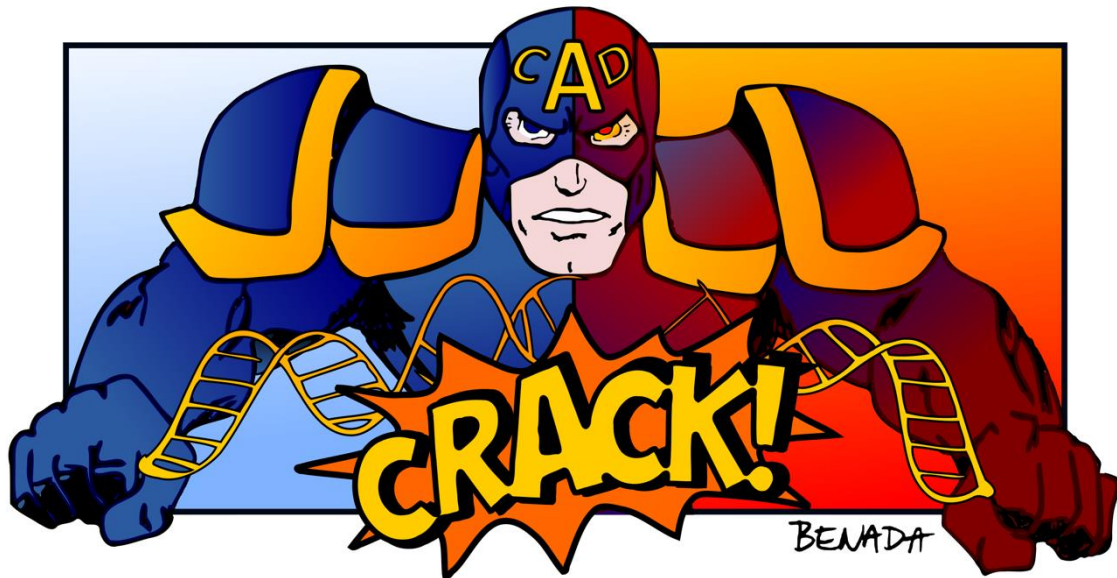


Illustration showing the function of the CAD enzyme that specifically breaks DNA. (Author: J. Benada)

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