Promising cancer therapy advanced by chemical explanation

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Radiation therapy: A chilling word that creates images of burn-injuries where the cancer killing ray went through the skin. For decades research hospitals have been investigating the alternative method Hadron therapy, or particle therapy, where runaway cells are bombarded with "naked" atomic nuclei or protons. When the particles pass through sick cells the collision creates chemical reactions preventing further cell division. Now researchers at the Department of Chemistry, University of Copenhagen, have discovered an unknown reaction caused by the therapy.

In the ten percent most important results of 2015

Birgitte Olai Milhøj is a PhD student at the Department of Chemistry.

Her results have been published in the periodical *Chemistry - A European Journal* in an article entitled "Insight into the mechanism of the Initial reaction of a OH-Radical with DNA/RNA nucleobases: a Computational Investigation of Radiation Damage". The article received special mention as one of the ten percent most important results in 2015.

Correct dose imperative to avoid damage

On paper, particle therapy is less damaging than traditional radiation therapy but in order to determine the size of doses, it is imperative to understand the chemical as well as the physical and biological processes triggered by the subatomic particles, say Milhøj's supervisor Professor Stephan Sauer.

"The therapist obviously needs to shoot as many particles as necessary but preferably so few that there is no subsequent damage. As they are, our new results cannot be used to calculate the correct doses but we have provided new insights into how the treatment functions at the molecular level. It is our hope that physicians will be able to develop this into a dosis calculator", says Sauer and goes on: "In the long run, I really hope that cancer patients will receive better treatment thanks to our efforts".

"Hungry" molecules tear DNA to pieces

When atomic nuclei collide with structures inside the cancer cell, so called OH-radicals are created. OH-radicals are water molecules (H2O) lacking an Hydrogen-atom thus having transformed into a H1O. Molecules like these are extremely "hungry" to regain the missing hydrogen-atom, explains Sauer.

"To a water molecule, losing one of its hydrogen atoms is almost as bad as it would be for me to lose an arm. The OH-radical will do almost

anything to steal a new hydrogen atom from anywhere. This might be from the cell's DNA-string, where there are abundant hydrogen atoms in the base pairs. If you destroy the base pairs, you prevent the cell from breeding. That is why it is so efficient to create these very aggressive OH-radicals inside the cancer cells", says Sauer.

Months of calculations for every possible reaction path

Milhøj and Sauer have uncovered the surprising reaction by pure computational chemistry but even in a computer, the calculations are extremely fiddly work. The further fate of the DNA base pairs is extremely dissimilar dependent on whether the OH-radical screeches in from above, below or from one of the sides. Consequently, Milhøj had to draw and animate the molecules in the computer and then switch on calculations lasting two to three months. All this in order to predict the consequences of just one single angle of attack, and she had to calculate 200 possible angles. The great breakthrough came to Milhøj when she developed a method of calculation reducing the time taken for each of the comprehensive simulations to two to three weeks for each of the 200 angles.

The first experiments with the new therapy go back as far as 1969 but not until the early noughts did hospitals throughout the world start adopting the therapy and invest in the machinery for it.

More information: Birgitte O. Milhøj et al. Insight into the Mechanism of the Initial Reaction of an OH Radical with DNA/RNA Nucleobases: A Computational Investigation of Radiation Damage, *Chemistry - A European Journal* (2015). DOI: 10.1002/chem.201503107

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