DNA damage: The dark side of respiration

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(Phys.org) —Adventitious changes in cellular DNA can endanger the whole organism, as they may lead to life-threatening illnesses like cancer. Researchers at LMU now report how byproducts of respiration cause mispairing of subunits in the double helix.

The DNA in our cells controls the form and function of every cell type in our bodies. The instructions for this are encoded in the linear sequence of the four subunits found in DNA, the bases adenine (A), cytosine (C), guanine (G) and thymine (T). Random changes in the sequence can lead to cell dysfunction, and may result in unrestricted cell proliferation and malignancies. Mutations can be induced by a variety of agents. For example, cellular respiration, i.e. the reduction of inspired oxygen to water, which powers cell function, also generates highly reactive oxygen species that can damage DNA, with the purine bases G and A being particularly susceptible to this kind of attack.

"Reactive oxygen species are responsible for two different sorts of DNA damage, as they induce formation of both 8-oxo-G and FaPy-G," says Professor Thomas Carell of the Department of Chemistry at LMU. In 2004, work done by Carell and his team defined how 8-oxo-G generates mutations. However, the basis for the mutagenic effect of FaPy-G has remained obscure – until now. In their latest publication, Carell and his colleagues describe how FaPY-G leads to mispairing of bases in the double helix.

Pernicious partner swapping

One G in one strand of the double helix normally matches up with a C on the other, forming a G:C pair. But as a consequence of damage by reactive oxygen species, the guanine base may be transformed into FaPy-G, so that we get a FaPy-G:C base pair. "We have now shown that, in the course of DNA replication prior to cell division, FaPy-G interacts with adenine, leading to the formation of FaPy-G:A base pairs. This partner swap is unusual, since unmodified guanine normally does not team up with adenine," Carell notes.

FaPy-G is subsequently recognized as abnormal and is removed by DNA repair enzymes. The missing base is replaced by a T – which is the usual partner for A. The net result is that the original G:C base pair has been converted into an A:T pair, and the base sequence has undergone a potentially dangerous mutation.

This outcome is made possible by the fact that the cell's damage-control systems find it surprisingly difficult to distinguish the normal guanine base from its aberrant derivative FaPy-G during DNA replication. "That this defect then leads to mispairing with adenine is one of the main reasons for the spontaneous development of tumors," says Carell. "So with every breath we take, our risk of getting cancer goes up by a teeny-weeny bit." Further insights into the reasons why FaPy-G often eludes the cell's detection and correction systems could help to improve the treatment of cancer, as the inhibition of DNA repair processes in tumor cells increases their sensitivity to chemotherapeutic drugs.

The research is published in *Nature Chemistry Biology*: www.nature.com/nchembio/journa … l/nchembio.1254.html

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