Novel UV-mediated mode of DNA repair

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UV light damages DNA. But LMU researchers now show that it can also mediate non-enzymatic repair of one type of damage, albeit in a specific context. This effect may have played vital role in early evolution of living systems.

The ultraviolet fraction of sunlight triggers photochemical reactions in the DNA molecules that make up the hereditary material in our cells. These reactions can result in alterations in the DNA structure which lead to mutations that may cause cell death or promote tumorigenesis. LMU researchers led by Professor Thomas Carell, who holds the Chair of

Bioorganic Chemistry, and Wolfgang Zinth, Professor of Biomolecular Optics, have now shown that the DNA itself can repair one of the most common types of UV-mediated damage by a non-enzymatic mechanism which is itself dependent on UV. The new findings appear in the *Journal of the American Chemical Society*.

Cells possess a variety of complex, enzyme-based mechanisms which are used for the repair of damaged DNA, and this year's Nobel Prize in Chemistry was awarded to three researchers for work on the elucidation of these mechanisms. The team led by Zinth and Carell, have now discovered the first instance of a sequence-dependent repair mechanism which does not require the participation of enzymes at all.

Sequence-specific repair

The DNA double helix consists of two spiral strands that are wound around one another. This structure is held together by interactions between the so-called bases – planar structures which project from each strand. The bases on opposite strands can pair up with one another in specific ways by forming so-called hydrogen bonds that stabilize them: every adenine base (A) pairs with a thymine (T) in the opposite strand, and every guanine (G) with cytosine (C). This base-pairing mechanism is a crucial element in the process of DNA replication.

The most common type of damage produced by the interaction of UV radiation with DNA is the so-called cyclobutane-pyrimidine dimer (CPD), in which adjacent thymines in the same strand are linked together. But UV light also generates short-lived, charged, and highly reactive chemical species called radicals between neighboring bases in the same strand, as Zinth and Thomas Carell demonstrate in the new paper. "It had been thought that these pairs of radicals go on to induce further damage. However, we have now shown that radical pairs formed between specific base combinations can actually repair damage that has

already taken place," says Wolfgang Zinth. The driving force for the repair process is supplied by the bases involved. Pairs of radicals formed next to a CPD are able to repair it by means of a charge-transfer process.

"In contrast to all other known repair mechanisms, this mode of repair is intrinsic to the DNA itself. It does not depend on the intervention of enzymes, as in all other known cases," says Thomas Carell. However, the novel mechanism is highly context-dependent and works only on a small collection of DNA sequences. The researchers have shown that it operates on the sequence GATT (when the TT sequence forms a CPD), and are now planning a systematic search to identify all sequence contexts in which the mechanism operates.

Possible role in prebiotic evolution

This discovery reveals that UV light has a dual effect on DNA. The radiation is not only deleterious, it can also provide a means of reversing some of the damage it causes. This hitherto unknown mechanism could have played a crucial role in the early evolution of living systems. "Sequences that are capable of self-repair are effectively more resistant to intense UV radiation than others. In prebiotic times, when the first strands of nucleic acids were being assembled into functional sequences, the Earth's surface was constantly exposed to a very high flux of UV. This probably acted as a major selection factor during the period in which the first viable protobiological structures emerged, and must have had a decisive effect on their evolution," says Wolfgang Zinth.

More information: Dominik Benjamin Bucher et al. UV-Induced Charge Transfer States in DNA Promote Sequence Selective Self-Repair, *Journal of the American Chemical Society* (2015). DOI: 10.1021/jacs.5b09753

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