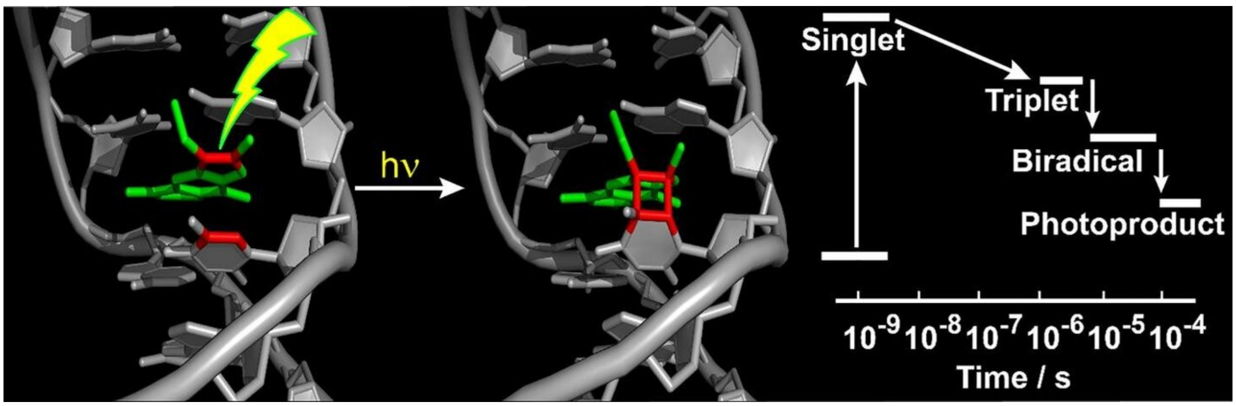
Shedding light on the reaction mechanism of PUVA light therapy for skin diseases

August 20 2019



Reaction stages when a psoralen molecule binds to DNA. The result is that the psoralen is permanently bound to the DNA via a cyclobutane ring. The cell is altered and thus damaged, and triggers the process of programmed cell death. Credit: ACS/Janina Diekmann

The term "PUVA' stands for 'psoralen' and 'UV-A radiation.' Psoralens are natural plant-based compounds that can be extracted from umbelliferous plants such as giant hogweeds. Plant extracts containing psoralens were already used in Ancient Egypt for the treatment of skin diseases. Modern medical use began in the 1950s. From then on, they were applied for light-dependent treatment of skin diseases such as psoriasis and vitiligo. From the 1970s onwards, PUVA therapy was used to treat a type of skin cancer known as cutaneous T-cell lymphoma.

Psoralens insert between the crucial building blocks (bases) of DNA, the hereditary molecule. When subjected to UV radiation, they bind to thymine—a specific DNA base—and thus cause irreversible damage to the hereditary molecule. This in turn triggers programmed cell death, ultimately destroying the diseased cell.

Researchers working with Prof. Dr. Peter Gilch from HHU's Institute of Physical Chemistry have now collaborated with Prof. Dr. Wolfgang Zinth's work group from LMU Munich to analyse the precise mechanism of this binding reaction. They used time-resolved laser spectroscopy for this purpose.

They found that—after the psoralen molecule has absorbed UV light—the reaction takes place in two stages. First, a single bond between the psoralen molecule and thymine forms. A second bond formation then yields a four-membered ring (cyclobutane) permanently connecting the two moieties (see figure). The researchers in Düsseldorf and Munich were also able to demonstrate that the first stage takes place within a microsecond, while the second needs around 50 microseconds. They compared this process with the damaging of the 'naked' DNA by UV light. That process also frequently results in cyclobutane rings, but the process takes place considerably faster than when psoralens are present.

Prof. Gilch explains the background to the research: "If we can understand how the reactions take place in detail, we can change the psoralens chemically in a targeted way to make PUVA therapy even more effective." Together with his colleague in organic chemistry, Prof. Dr. Thomas Müller, he wants to develop these high-performance psoralen molecules at HHU within the scope of a DFG project.

More information: Janina Diekmann et al, The Photoaddition of a Psoralen to DNA Proceeds via the Triplet State, *Journal of the American Chemical Society* (2019). DOI: 10.1021/jacs.9b06521

Provided by Heinrich-Heine University Duesseldorf