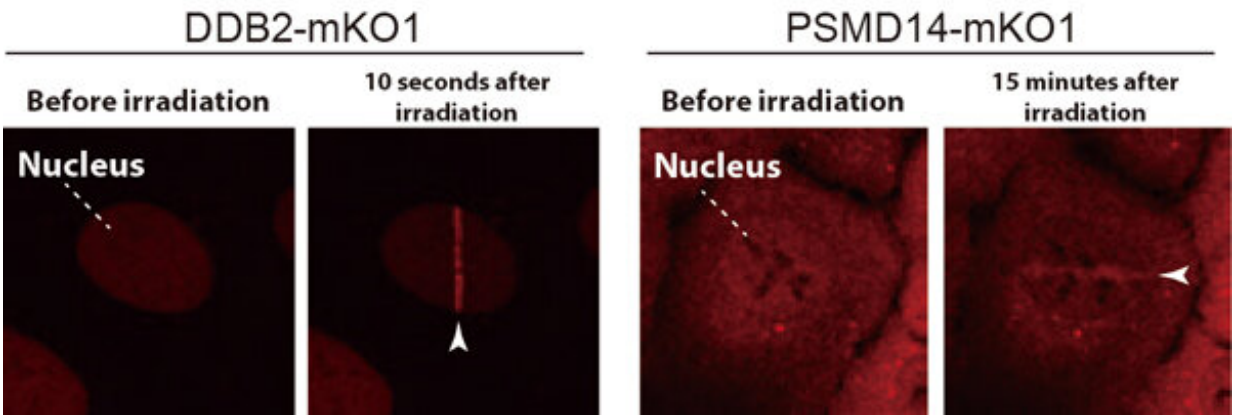
New findings shed light on the repair of UV-induced DNA damage

December 8 2020



Credit: Kobe University

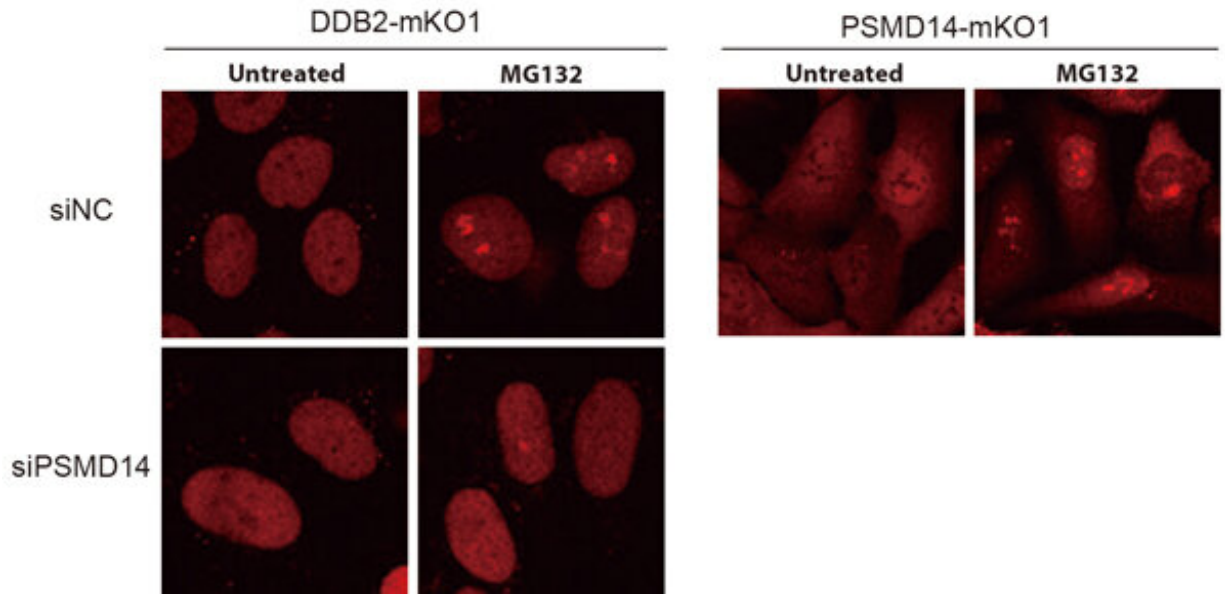
An international research team has clarified the regulatory mechanism of the ubiquitin-proteasome system in recognizing and repairing DNA that has been damaged by ultraviolet (UV) light. The investigators at Kobe University (Japan), the National Institute of Health Sciences (Japan), the Catholic University of Louvain (Belgium), Kyoto University (Japan), and the National Institute of Genetics (Japan) have published their results in the journal *Scientific Reports*.

UV light from the sun is very harmful to living organisms because it can damage their genes. This is called DNA damage and normally it is fixed by the repair system in our cells, preventing us from experiencing

adverse effects resulting from exposure to sunlight during the course of our daily lives. However, patients with xeroderma pigmentosum (XP) are born with malformations in this repair system, which means that their bodies are unable to sufficiently repair DNA damage caused by UV light. Consequently, they are predisposed to developing skin cancer in sun-exposed areas.

Intracellular proteins are generated and degraded as required, and the ubiquitin-proteasome system is known to play an important role in managing this degradation process. It has been previously shown that the ubiquitin-proteasome system coordinates cellular responses to repair the UV-induced DNA damage. However, the detailed mechanism behind this had not been clarified until now.

The international team, led by Prof. SUGASAWA Kaoru at the Biosignal Research Center, Kobe University, developed a custom microscope system which allowed them to successfully observe the dynamic behaviors of various intracellular proteins in response to UV-induced DNA damage (Figure 1, left).



Inhibiting proteasome with MG132 causes both DDB2 and proteasome to accumulate in the vicinity of the nucleoli. However, this aggregation can be alleviated by suppressing PSMD14 expression. Credit: Kobe University

The DDB2 protein is one of the gene products responsible for XP and is important for recognizing UV-induced DNA damage. Utilizing the custom microscope system enabled the researchers to make a new discovery: they found that the DDB2 protein works together with the ubiquitin-proteasome system to promote DNA repair. First of all, the multi-protein complexes, proteasomes, quickly accumulated at DNA damage sites depending on the presence of DDB2 proteins. This suggests that the proteasome's protein degradation function could be activated following the damage recognition and repair.

Furthermore, using an inhibitor to suppress this proteasome activity caused the proteasome to accumulate in a specific region of the nucleus, trapping the DDB2 protein and making it unable to participate in DNA damage repair. On the other hand, suppressing the expression of proteasome subunits compromised proper assembly of the proteasomes and the aforementioned proteasome aggregation was no longer observable. However, the absence of proteasomes severely suppressed the accumulation of DDB2 proteins at DNA damage sites.

These results revealed for the first time that proteasomes' protein degradation activity and architectural integrity are involved in the regulation of DDB2 protein-mediated DNA damage repair via separate mechanisms.

The results of this study show that the action of the DNA damage

recognition mechanism is essential for enabling DNA damage to be efficiently repaired. Furthermore, this understanding will also contribute towards clarifying the onset mechanisms of diseases such as skin cancer, in addition to the development of treatments to suppress this onset.

More information: Wataru Sakai et al, Functional impacts of the ubiquitin–proteasome system on DNA damage recognition in global genome nucleotide excision repair, *Scientific Reports* (2020). DOI: 10.1038/s41598-020-76898-2

Provided by Kobe University