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Ubiquitin signals in DNA repair

An exciting discovery reported in *Science* (16.12.2005, pages 1821-1824) may significantly improve our understanding about the molecular basis of DNA repair. Scientists at the Institute of Biochemistry II, Goethe University Medical School in Frankfurt and their collaborators describe a key cellular switch that instructs the cell how to respond to DNA damage. When DNA is damaged, for example by ultraviolet (UV) rays from the sun, the DNA lesions hinder the vital process of DNA replication. To get round the lesions, the cell has to employ special enzymes called translesion polymerases. The scientists have shown that the ability of these polymerases to bind to a small protein called ubiquitin is crucial for their ability to replicate past the damaged DNA. This study provides a long-sought clue on how translesion polymerases can gain preferential access, when the enzymes that normally copy DNA get stuck at the sites of DNA damage.

“This crucial switch is disturbed in patients with the variant form of Xeroderma pigmentosum, a UV-induced skin syndrome, leading to accumulation of DNA damage and skin tumor development” explains Ivan Dikic, a senior author on this study and professor in the Institute of Biochemistry II.

“Our collaborative study has given us exciting new insights into understanding the ways in which our cells deal with damage to our genetic material” says a pioneer in the DNA repair field and a co-author Alan Lehmann, Chairman of the Genome Damage and Stability Centre at the University of Sussex, UK.

By combining experimental and bioinformatical approaches, the scientists identified two new kinds of structures or “domains”, called UBM and UBZ, which are found in enzymes that bind ubiquitin. Matthias Peter and his colleagues at the Eidgenössische Technische Hochschule Zürich (ETHZ) in Zurich, used nuclear magnetic resonance (NMR) to map the surface of the UBM domain that binds the ubiquitin.

Identification of the Ub-interactome, the network of proteins that bind to other proteins that are tagged with ubiquitin, is the basis for better understanding of many cellular functions. “Defining protein domains that specifically bind to ubiquitin and the way in which they interact inside cells are currently major challenges in the field of ubiquitin signaling” says a co-author and bioinformatics specialist Kay Hofmann at the Miltenyi Biotec GmbH, Cologne, Germany.

The scientists were quite surprised to find that these novel ubiquitin-binding domains are present in a large panel of proteins involved in cell signalling, immune responses, DNA transcription and DNA repair. “This indicates a broader and more general importance of ubiquitin signaling in regulation of cell functions and suggests that their deregulation may contribute to disease development. Detailed understanding of these principles may help in improving human therapy,” says Dikic.

Werner Müller-Esterl, Director of the Institute of Biochemistry II in Frankfurt emphasizes that the success of this project is embedded in an international and interdisciplinary environment created around it. “Their findings mark an important step forward towards a deeper understanding of the mechanisms securing replication fidelity, with important implications for the development of novel drugs for human diseases caused by deficient DNA repair mechanisms”.

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