**The molecular basis for UV-damage recognition in chromatin**

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DNA in each cell is constantly exposed to several environmental and endogenous threats. This leads to a variety of DNA mutations that occur spontaneously (i.e., replication errors), after exposure to reactive chemical intermediates (i.e., reactive metabolites), or following exposure to UV-light. The global genome repair (GGR) pathway surveils genomic DNA for UV-light induced pyrimidine dimers, and targets these for repair by the nucleotide excision repair (NER) pathway (Ref. 1). Cyclo-butane pyrimidine dimers (CPDs) and pyrimidine-pyrimidone 6-4 photoproducts (6-4PP) are found throughout the genome, including regions of chromatin, and are detected by the UV-damaged DNA binding proteins (UV-DDB complex), comprised of DDB1 and DDB2. How DNA lesions are sensed when embedded within nucleosomes, with histones and the two DNA gyres potentially restricting accessibility to the damage, is unclear at present.

We set out to investigate structurally and biochemically how the UV-DDB complex binds damaged nucleosomes around the sites where the minor groove points outward, a location where CPDs are frequently found following UV-irradiation in model systems in vivo, and cell lines (Ref. 2). We present atomic resolution cryo-EM structures of UV-DDB in complex with nucleosomes containing 6-4PP or abasic sites that detail UV-damage recognition at different sites. We find that the recognition of more distal lesions from the most populated CPDs site is not possible on strongly positioned nucleosomes. We describe how UV-DDB recognizes UV-induced damage in chromatin, and the emerging role of nucleosome positioning strength in DNA damage recognition.

Our study provides the molecular basis for UV-damage detection by UV-DDB in chromatin, and offers a conceptual framework for DNA sequence/damage detection by diverse DNA binding proteins, including transcription factors.

References

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