【Grant-in-Aid for Scientific Research (S)】

Integrated Disciplines (Environmental Science)

Title of Project : Molecular mechanisms underlying higher-order regulation of DNA damage recognition for nucleotide excision repair

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Research Project Number : 16H06307 Researcher Number : 70202124
Research Area : Risk sciences of radiation and chemicals
Keyword : DNA damage recognition, nucleotide excision repair, xeroderma pigmentosum

【Purpose and Background of the Research】

Genomic DNA is highly susceptible to damage derived from various sources. Nucleotide excision repair (NER) eliminates diverse DNA lesions caused mainly by environmental agents, such as ultraviolet light (UV) and chemical compounds, thereby playing a crucial role in preventing various diseases including cancer.

In mammalian NER, the xeroderma pigmentosum-related factors, XPC and DDB2, recognize and bind to sites of damage and initiate the repair reaction. Although these damage recognition factors exhibit specific binding affinities for damaged DNA *in vitro*, precise molecular mechanisms still remain to be elucidated, by which a relatively small number of lesions can be efficiently recognized *in vivo* within the huge genomic DNA.

This project is aimed to elucidate novel molecular mechanisms underlying higher-order regulation of the intiation step in NER, particularly by focusing on intracellular dynamics and interactions of XPC and DDB2 proteins. This research will contribute to understanding of the molecular basis that enables efficient surveillance of genomic DNA in response to various environmental stresses.

【Research Methods】

This project undertakes three approaches to identify novel factors and molecular mechanisms involved in regulating the initiation of NER; 1) comprehensive identification of interacting partners of XPC and DDB2, 2) search for siRNA and chemical compounds that affect recruitment of XPC or DDB2 to local UV damage (Fig. 1), 3) identification of biochemical activities that stimulate the cell-free NER reaction reconstituted with purified NER factors and damaged DNA substrates organized into chromatin structures. Candidate factors obtained from these approaches will be tested for their functions in NER by up- or down-regulation of their expression. Finally, the underlying molecular mechanisms will be analyzed with the defined cell-free NER system.

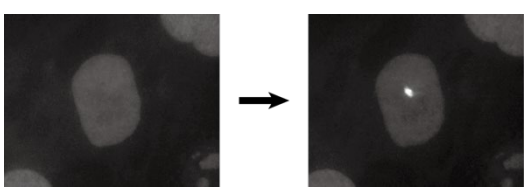

Fig. 1. Visualized accumulation of EGFP-tagged XPC in the area of local UV damage

【Expected Research Achievements and Scientific Significance】

DNA damage recognition is a crucial, rate-limiting step regulating the entire repair process. Identification of novel factors and mechanisms that stimulate this critical step would be expected to lead to enhancement of our intrinsic NER capacity, which will be applied to developing strategies for protection against UV and chemicals, and also for prevention of various diseases including cancer.

【Publications Relevant to the Project】

Akita M, Tak YS, Shimura T, Matsumoto S, Okuda-Shimizu Y, Shimizu Y, Nishi R, Saitoh H, Iwai S, Mori T, Ikura T, Sakai W, Hanaoka F, Sugasawa K: SUMOylation of xeroderma pigmentosum group C protein regulates DNA damage recognition during nucleotide excision repair. Sci. Rep. 5, 10984 (2015).

Matsumoto S, Fischer ES, Yasuda T, Dohmae N, Iwai S, Mori T, Nishi R, Yoshino K, Sakai W, Hanaoka F, Thomä, NH, Sugasawa K: Functional regulation of the DNA damage-recognition factor DDB2 by ubiquitination and interaction with xeroderma pigmentosum group C protein. Nucleic Acids Res. 43, 1700-1713 (2015).

【Term of Project】 FY2016-2020

【Budget Allocation】 133,500 Thousand Yen

【Homepage Address and Other Contact Information】

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