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

Structural studies for understanding the mechanism of DNA repair in chromatin

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Project Information	Project Number : 23H05475 Project Period (FY) : 2023-2027 Keywords : DNA repair, chromatin, cryo-EM, IR, UV

Purpose and Background of the Research

●Outline of the Research

Our genome is conserved over generations, as our genetic information is stably maintained. However, there are many environmental factors that damage the genetic information. Representative factors are ionizing radiation (IR) and ultraviolet radiation (UV), both of which induce deleterious damages to DNA (Figure 1). These DNA damages are extremely harmful, leading to genetic mutations and cancer. To respond to these DNA damages, living organisms have developed the mechanism called “DNA repair” by which DNA damages are corrected. In the DNA repair system, repair factors quickly search and remove DNA lesions from the genome, thus functioning as a primary defense mechanism against IR and/or UV. However, how DNA repair works in our cells remains unknown.

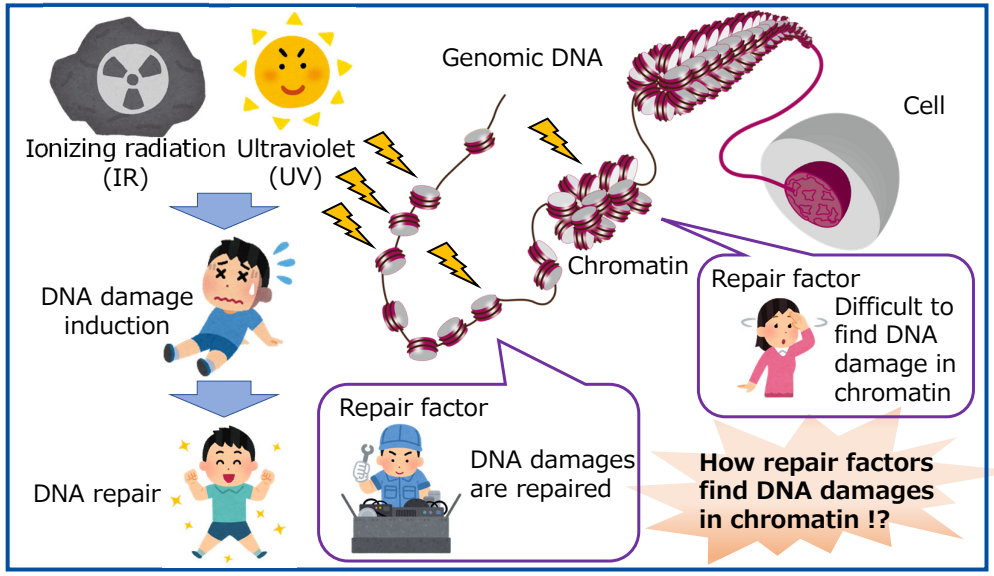

Figure 1. Image of DNA repair system and chromatin structures

●DNA repair system and chromatin structures

Our genome is maintained in each cell, and most cells conserve the same genomic sequence. Chromatin is a structure consisted of DNA and proteins, allowing cells to pack the entire genome in nucleus (Figure 1). Due to its firm packing, chromatin seems to conceal DNA lesions from DNA repair factors, and yet the DNA repair system nevertheless functions effectively in chromatin. We are fascinated by this phenomenon and taking up the challenge to understand the mechanism by which DNA repair machinery finds DNA lesions in chromatin.

●Effects of DNA repair defects

Congenital defects in the DNA repair system cause serious genetic disorders such as Cockayne syndrome and xeroderma pigmentosum. When exposed to excessive amount of IR or UV, even in persons whose DNA repair system is fully functional, other forms of DNA repair-related disorders can occur. Exposure to high doses of IR induces cleavage of genomic DNA and leads to cell death. Exposure to high doses of UV causes mutations in our genome and triggers cancer development (Figure 2).

●Research purpose

In this study, our purpose is to reveal how DNA repair system functions in chromatin by cryo-electron microscopy (cryo-EM).

Expected Research Achievements

●Analyses of DNA repair machinery

IR or UV induces cleavage or distortion in DNA structure. In IR damage repair, repair factors recognize DNA cleavage and recruit other factors to proceed with the repair process. In UV damage repair, other repair factors recognize UV damage and proceed to damage extraction and new DNA synthesis. In both cases DNA repair machinery functions efficiently in chromatin, in which DNA is tightly packed. The aim of this research is to reveal the basis of DNA repair mechanism in chromatin by cryo-EM.

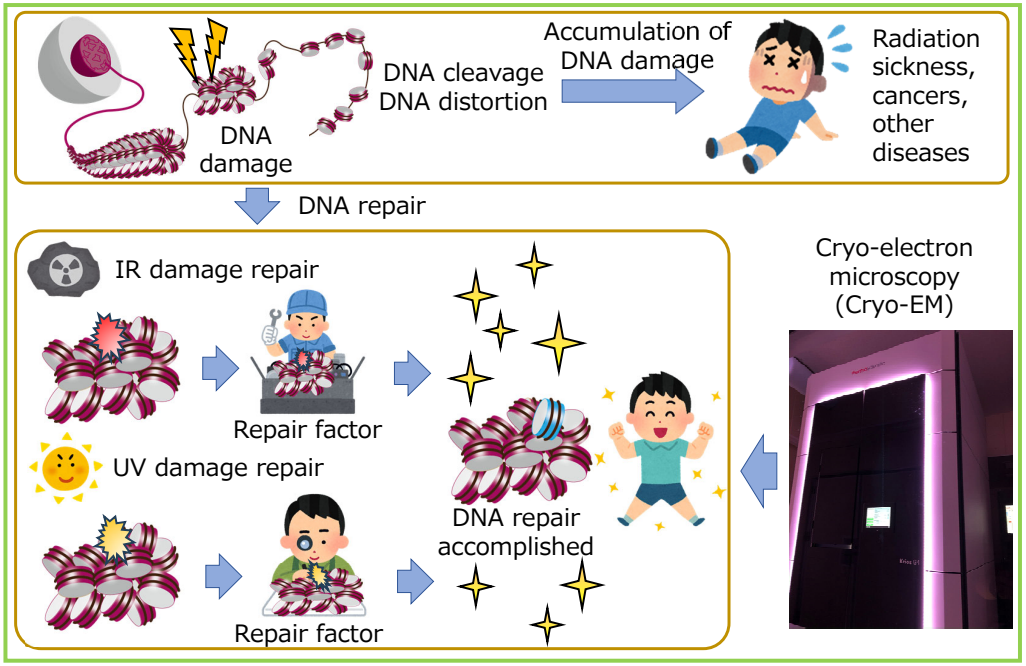

Figure 2. Image of this research for DNA repair

●Research impact on public services

Our research achievements will contribute to the development of clinical treatments for genetic diseases caused by the DNA repair defects. Our findings could also accelerate the developments of risk management strategies against IR and/or UV.

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