Title of Project : To investigate the mechanism(s) of chromatin remodeling involved in the coupling of repair to replication and transcription

Term of Project : FY2010-2014

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【Purpose of the Research Project】

It is well established that dynamic changes in chromatin structure are essential for extracting (transcription) and for copying (replication) the genetic information in eukaryotic cells. More recently, the dynamic behavior of chromatin was also recognized as important for healing DNA lesions (repair). DNA lesions are detected by chromatin at first, and then the information is transmitted to repair proteins. To further elucidate the mechanism of DNA damage responses, we will focus on the dynamic behavior of chromatin at DNA lesions, which will have far-reaching implications for the understanding of genetic disease. Our goal is to investigate the mechanism(s) of chromatin remodeling involved in the coupling of repair to replication and transcription.

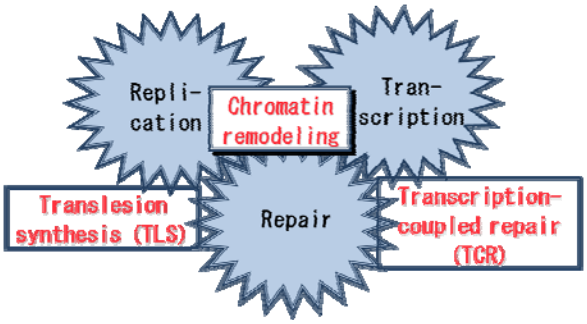

Figure 1 Schematic representation of this project

【Content of the Research Project】

1) Studies on chromatin remodeling caused by histone modification: Recent studies have revealed that histones are post-translationally modified at various residues by methylation, acetylation, phosphorylation, ubiquitylation, ADP-ribosylation and so forth under various cellular conditions. We will focus on these histone modifications with special reference to replication, transcription, and repair.

2) Analyses of chromatin remodeling mechanisms and their implications for the understanding of various diseases: Recent studies have revealed that defects in certain chromatin remodeling factors cause cancer. We will identify and characterize these proteins, in the hope to finding or developing novel drugs that sensitize cells to chemotherapeutic agents. Analyses of the structure of these proteins will help to develop more specific drugs.

3) Couplings of repair to transcription and replication: The transcription-coupled repair mechanism is known to prevent apoptosis, which reduces the incidence of neural diseases. Translesion synthesis prevents cancer by allowing the replication apparatus bypass DNA lesions during DNA replication. Up to now, these mechanisms have been studied in cell-free systems with only naked DNA. We will make use of reconstituted chromatin to unravel how chromatin remodeling affects these repair processes and how chromatin structure contributes to the coupling or repair to replication and transcription.

【Expected Research Achievements】

An accurate and detailed analysis of replication, repair and transcription within the context of the chromatin template will provide new insights into how DNA metabolism is affected by chromatin structure and dynamics. Additionally, it opens the perspective of discovering mechanism(s) in chromatin that commonly regulate these fundamental transactions on DNA. This could lead to the development of novel chemotherapy sensitizing drugs that target these mechanisms.

【Key Words】

Chromatin remodeling: Dynamic structural changes to the chromatin occurring throughout the cell division cycle.
Proteomics: The large-scale study of proteins, particularly their structures and functions.

【Homepage Address】

http://www.rbc.kyoto-u.ac.jp/shingakujutsu/repair/index.htm